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TREASURY DEPARTMENT
Public Health and Marine-Hospital Service of the United States

HYGIENIC LABORATORY.—BULLETIN No. 47

OCTOBER, 1908

STUDIES ON THYROID

I.—THE RELATION OF IODINE TO THE PHYSIOLOGICAL ACTIVITY OF THYROID PREPARATIONS

By

REID HUNT

and

ATHERTON SEIDELL

WASHINGTON
GOVERNMENT PRINTING OFFICE
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STUDIES ON THYROID: I. THE RELATION OF IODINE TO THE PHYSIOLOGICAL ACTIVITY OF THYROID PREPARATIONS.

By Reid Hunt,
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INTRODUCTION.

Thyroid is a unique drug and occupies a place in therapeutics which can not be filled, even imperfectly, by any other known therapeutic agent. Its use was the first practical application of the doctrine of internal secretion and it still remains the most striking example of the conscious utilization, for therapeutic purposes, of an "hormone."

Although much has been learned in recent years in regard to the function of the thyroid as a glandular organ and also as to the effects of the administration of thyroid preparations upon the organism, both in health and in disease, little progress has been made in the study of thyroid as a drug. The "active principle" of the gland is unknown, and there are no generally accepted means, aside from actual clinical tests, of determining the relative value of different thyroid preparations.

A very important advance in our knowledge of thyroid as a drug was made when Baumann[a] discovered in 1895 that the gland usually contains iodine. Since that time the chief interest in the chemistry of the thyroid has centered around this iodine, but the opinions as to the physiological significance of the latter are as far apart to-day as they were twelve or thirteen years ago.

The question of the relation of the iodine to the physiological activity of thyroid is from the pharmacological standpoint the most important problem connected with this drug; this is the subject of the present bulletin.

[a] E. Baumann, Ztschr. f. physiol. chem., Strassb., 1895–96, **21**, p. 319.

Before considering the main problem, however, a few words may be devoted to certain phases of the older history of the thyroid. The relation of iodine to this gland had been for many years a matter of interest to physicians and was much discussed even before Baumann's important discovery. It has long been recognized that iodine has some special relation to the thyroid. Seven years after the discovery of the element iodine by Courtois, in 1812, Straub, of Berne, suggested that it was the active principle of the "toasted sponges" (Spongia "usta" or "tosta") and the "Aethiops vegetabilis," which had been used in the treatment of goiter at least since the thirteenth century.[a] Since 1820 iodine, as such or in combination, has been in constant use in the treatment of diseases of the thyroid.

About the middle of the last century great interest was aroused by the work of Chatin, Marchand, and others on the relation of iodine in drinking water to goiter. The more recent history of this subject began with the revival of interest in the physiology and pathology of the thyroid gland which was stimulated by the work of Gull and Ord on myxoedema and of Kocher and Reverdin on the effects of the removal of the thyroid in man. This work was followed, partly as a result of the stimulus of Brown-Sequard's ideas concerning internal secretion, by the introduction of organotherapy in the treatment of diseases of the thyroid. The brilliant results of this form of treatment led to the search for an "active principle," and this work culminated in the discovery of iodine in the thyroid by Baumann. In the year of Baumann's discovery Kocher,[b] who had been much impressed by the similarity of the effects of iodine and thyroid in the treatment of goiter, had suggested the desirability of examining the thyroid for iodine; the tests made in Berne were, however, negative.

Baumann at first considered the iodine containing substance which he isolated and called iodothyrine to be the active principle of the thyroid; although he recognized later that in the gland much of this iodothyrine is in combination with proteins, neither he nor his coworkers seemed to have entertained any doubt that the iodine was very important for the physiological activity of the thyroid.

Following Baumann's discovery, determinations of the amount of iodine were made in the thyroid in a great variety of conditions; the influence of health, disease, sex, pregnancy, age, locality (near or remote from the sea, on the plains, and in the mountains), diet, climate, etc., was investigated. The amount of iodine in the thyroids of a great variety of animals was also determined. Far-reaching conclusions were drawn from such studies, especially as regards the relation of iodine to the diseases of the thyroid itself (various forms of

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[a] *cf.* E. Harnack, München. med. Wchnschr., 1896, **43,** p. 196; G. Monéry, Fonction iodeé de la glande thyroide, Thesis, Lyons, 1903; Th. Kocher, Die Therapie des Kropfes, Deutsche Klinik, Berl. and Wien, 1905, **8,** p. 1115.

[b] Th. Kocher, Cor. Bl. f. schweiz. Aerzte, 1895, **25,** p. 3.

goiter) and to various forms of insanity. A vast number of data were collected, but these were often contradictory and not easily correlated.

The result was that within a few months after Baumann's first publication on the subject objections began to be urged against the view that the iodine is an important constituent of the thyroid. These objections have been repeated and still others urged up to the present time; they will be considered in detail in the following pages.

Part I.

THE PARALLELISM BETWEEN THE PHYSIOLOGICAL ACTIVITY AND THE IODINE CONTENTS OF THYROID.

A. HISTORICAL.

The views as to the relation of the iodine to the physiological activity of the thyroid may be classified under three heads: (1) Some investigators hold that the activity of thyroid is directly proportional to and dependent upon its iodine content and that thyroid free of iodine has no physiological activity. (2) There is another group of writers who take the view that there is no relation between the physiological activity of thyroid and its iodine content and that no importance should be attached to the iodine which is usually present in the thyroid. (3) Other writers admit that there is a parallelism between the physiological activity and the iodine content, but deny that the former is dependent upon the latter. Some of those holding this view apparently consider that the iodine is simply associated with the active part of the gland in some unknown, perhaps accidental, way. Others hold that the larger amount of iodine in active thyroid results from the activity of the gland itself; they consider that the more active the gland the larger the amount of iodine it is able to hold in combination. This latter view is closely connected with the theory that one of the functions of the thyroid is to take up injurious substances (including iodine) and to render them harmless.

Some of these theories have been combined. Thus von Cyon supposes the thyroid to take up iodine, by which process the latter is rendered harmless and at the same time a new compound, useful as an internal secretion, is formed.

We believe that these conflicting views have resulted partly from the failure of previous writers to recognize that thyroid free of iodine has a certain degree of physiological activity and partly from the fact that there has been a confusion of several distinct problems and that authors have often looked upon the subject from but a single point of view.

Baumann and some of the other earlier workers in this field apparently entertained no doubts as to the iodine being an important part of the "active principle" of the thyroid. They based this view upon the physiological action of iodothyrine in health and disease[a] and

[a]E. Baumann and E. Roos, Ztschr. f. physiol. Chem., Strassb., 1895–6, **21,** p. 487.

on the fact that iodine is so generally found in the thyroid in health and is apparently absent or present in diminished amounts in certain forms of goiter.

Before discussing in detail the chief arguments in favor of Baumann's view certain of the objections which have been made to it may be considered. The principle of these objections may be classified as follows:

a. Iodine is not invariably found in the thyroids of healthy animals; when it does occur there are great variations in its amount.

b. Artificially iodized proteins, including those of the thyroid itself, are inactive physiologically or the activity is not at all proportional to the amount of iodine which has been added; this is also true of iodothyrine to which iodine has been added *in vitro.*

c. Thymus was reported to be of value in the treatment of goiter.

d. The reputed "active principle" of the thyroid (Baumann's iodothyrine) did not prevent tetany in animals from which the thyroids had been removed.

e. Efficiency of iodine compounds other than iodothyrine in goiter.

These points may now be considered in more detail:

a. Iodine is not invariably present in the thyroid.—Miwa and Stoeltzner[a] early laid great emphasis on this point. They argued that if the theory that iodine is an essential constituent of the thyroid is correct, then the absence of iodine in the thyroid of an individual would have the same serious effects as the absence of the gland itself. They pointed out that Baumann had reported the frequent absence of iodine from the thyroid of children, and of dogs fed on meat; yet neither the children nor the dogs had shown any indications of thyroid insufficiency. Miwa and Stoeltzner confirmed Baumann's observations on the frequent absence of iodine from the thyroids of children; they also stated that the hen's egg contains no iodine and that the young chick thus begins life without iodine. They emphasized the dependence of the iodine content of the thyroid upon the diet. From these facts Miwa and Stoeltzner argued that the iodine usually found in the thyroid has no more significance than the traces of copper so often found in the liver. Similar arguments were advanced with great emphasis by Neumeister[b] at about the same time; he stated that the iodine of the thyroid has absolutely no physiological significance.

These arguments of Miwa and Stoeltzner and of Neumeister have been repeated to the present time; the facts upon which they were based have received abundant confirmation.[c] Thus Töpfer in Vienna

[a] S. Miwa and W. Stoeltzner, Jahrb. f. Kinderh., 1897, **45,** p. 83.

[b] R. Neumeister, Lehrbuch der physiologischen Chemie, 2d ed., 1897, p. 520. Cf. also Halliburton in Schäfer's Textbook of Physiology, 1898, **1,** p. 89.

[c] An abstract of the literature showing how frequently iodine is absent from the thyroids of infants is given on page 33 of this bulletin.

found no iodine in the thyroids of cattle.[a] Roos[b] found no iodine in the thyroids of three foxes; none in that of a polecat; none in that of a wild cat; he found it in but two of six martens; it was absent from the thyroids of four domestic cats and present in but traces, or in very small amounts, in those of five others; it was absent in four of eleven dogs, in two of four horses, and three of seven hogs.

In many cases the presence or absence of iodine is dependent upon the character of the food which the animal has received.

The thyroids of herbivorous animals, whose food usually contains small amounts of iodine, are almost always richer in this element than are those of carnivorous animals, whose food is usually poor in iodine.[c] Sheep pastured near the sea may have double the amount of iodine in their thyroid as those pastured in inland regions.[d] The amount of iodine in the thyroid of omnivorous animals (hog, dog, man) is especially variable. Nagel and Roos[e] found the percentage in the dried glands of hogs to vary from 0 to 0.075, although the glands were obtained from the same slaughterhouse.[f] Baumann found the percentage of iodine in the thyroid of horses to vary from 0.06 to 0.17.[g]

As a rule it is not possible to detect any difference between the animals which have a large percentage of iodine in their thyroids and those which contain none or only traces; removal of the gland is followed by as severe symptoms in the latter as in the former. Thyroid free of iodine seems to meet the needs of the body as well as the thyroid that contains iodine.[h]

Human thyroids also contain quite variable amounts of iodine, as was first pointed out by Baumann.[i] Jolin[j] has recently summarized the entire literature on the occurrence of iodine in the thyroid of man and has reported a very large number of analyses of such thyroids obtained in Sweden; he found great variations in the percentage of iodine and was unable to discover any constant relation between its presence or amount and conditions of health or disease. He asks, "Can not the great variations in the iodine content of not only pathologically altered thyroids but also of normal glands, and especially the fact that thyroids may be found in adults as well as in children which contain no iodine or scarcely traces of it, simply depend upon the fact that the iodine is an accidental constituent

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[a] Töpfer, Wien. klin. Wchnschr., 1896, **9,** p. 141.

[b] E. Roos, Ztschr. f. physiol. Chem., Strassb., 1899, **28,** p. 55.

[c] E. Roos, l. c.

[d] Th. Suiffet, J. de pharm. et chim., Par., 1900, [6] **12,** p. 50.

[e] W. G. Nagel and E. Roos, Arch. f. (Anat. und) Physiol., Suppl.-Bd., 1902, p. 267.

[f] A specimen of hog thyroid examined by us contained 0.33 per cent iodine.

[g] Baumann, Ztschr. f. physiol. Chemie, Strassb., 1896, **22,** p. 17.

[h] Exceptions to this will be referred to later.

[i] E. Baumann, Ztschr. f. physiol. Chem., Strassb., 1896, **22,** p. 1.

[j] S. Jolin, Festschrift, O. Hammarsten, Upsala, 1906.

(nebensächlicher Bestandteil) of the thyroid and its secretion?" He further states that the fact that in the body iodine is found chiefly in the thyroid "does not prove that the iodine is necessary for the activity of this gland; it may be explained by supposing that the thyroid has, among other functions, that of taking up an excess of iodine in the blood and storing it."

Several other recent writers have expressed somewhat similar views.[a] This point of view is, however, by no means new; Roos[b] referred to it in 1899 in the following words:

> To consider the accumulation of iodine in the thyroid as an accidental process which has no greater significance for the body than the storing up of certain metals in the liver seems to me to be a very unsatisfactory conception; for on it it is entirely unintelligible why the thyroid should use the iodine for the making of a substance (iodothyrine) which has such a marked effect upon metabolism and myxoedema instead of combining it in a much less active form, as occurs when iodine is allowed to react with proteins outside of the body.

Such studies as the above (they may be called statistical studies) have undoubtedly brought to light many facts, some of which are difficult to satisfactorily explain. Still they do not seem to us to weaken the conclusion that iodine is an important constituent of the thyroid. All the writers who have discussed this subject seem to have taken one of two extreme views—that iodine is necessary to any physiological activity, or that it has no part at all in rendering the thyroid active. No one seems to have suggested an intermediate view, viz, that thyroid free of iodine may have a certain degree of activity, although this is much less than that of thyroid containing iodine, until one of the present writers discovered that it is distinctly active in altering the resistance of animals to certain poisons.[c] This subject will be discussed in detail in the experimental part of this section. It will suffice for the present to state that we believe this conception and the conclusions that may be drawn from it go far toward answering the arguments for the unimportance of iodine which have been drawn from statistical studies.

b. Physiological inactivity of artificially iodized proteins and colloid.—The question of the relation of the iodine to the activity of the thyroid was approached experimentally by Hutchinson,[d] who prepared an artificial iodized nucleo-albumin from the thymus of calves. Samples of it contained from 4 to 7 per cent of iodine; it had no effect in myxoedema or upon the pulse, temperature, or weight of subjects to whom it was administered. Hellin[e] had previously found iodized

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[a] Bunge, Lehrbuch der Physiol. des Mensch., 2d ed., 1905, **2,** p. 631; S. J. Meltzer, N. Yorker med. Monatschr., 1907, **19,** p. 223; Abderhalden, Lehrbuch der physiol. Chem., 1907, p. 647.

[b] E. Roos, Ztschr. f. physiol. Chem., Strassb., 1899, **28,** p. 59.

[c] R. Hunt, J. Am. M. Ass., 1907, **49,** p. 1325.

[d] R. Hutchinson, J. Physiol., 1898–99, **23,** p. 181.

[e] D. Hellin, Arch. f. exper. Path. u. Pharmakol., Leipzig, 1897, **40,** p. 121.

albumin and nucleo-albumin prepared from the spleen to be inactive. Blum[a] had also found iodized albumin almost without effect upon metabolism. Hutchinson also increased artificially the percentage of iodine in colloid derived from the thyroid. Although such a product contained nearly ten times as much iodine as the original material, it had no greater physiological activity. Hutchinson drew the following conclusions from these results:

> One would conclude from the whole evidence that the iodine in the thyroid gland, if it plays an essential part in the activity of the latter at all, does so simply in virtue of the special form of combination in which it is present.[b]

Hutchinson had apparently concluded from earlier work that not much importance was to be attached to iodine as a factor in determining the activity of the thyroid. Thus in 1896 he wrote as follows:[c]

> It must not * * * be supposed * * * that the iodine is necessarily the essential factor in the activity of the thyroid gland. One has only to realize the small proportion in which it is normally present—only a few milligrams in a whole gland—to be convinced of that. * * * Baumann has himself failed to find any iodine at all in the thyroid of some children. Yet I suppose such a gland is none the less active.

Blum[d] and Roos[e] had also early pointed out that thyroid proteins or iodothyrine to which iodine had been added *in vitro* were physiologically inactive or less active than the natural products containing much less iodine. Blum used this observation as an argument against the view that the iodine is a factor in the physiological activity (or "toxicity," as Blum denies that the thyroid produces an internal secretion) of the proteins of the thyroid; he applied this view also to the iodine which has been taken up by the living gland, maintaining that the iodization *in vivo* is strictly analogous to that *in vitro*. Roos[f] endeavored to disprove Blum's theory by feeding iodine to dogs until the iodine content of the thyroid had been considerably increased; he stated that such thyroids showed increased physiological activity. Blum[g] points out that Roos's figures are hardly conclusive in this respect. We have recently studied this phase of the subject, using new methods for determining the activity of the thyroid, and have completely confirmed Roos's results. (See Part II of this bulletin.)

c. The value of thymus in goiter.—Further arguments against the view that the iodine is an important constituent of thyroid have been based upon the statements that thymus has an effect in goiter similar

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[a] F. Blum, München. med. Wchnschr., 1898, **45,** p. 270.

[b] Similar views have been expressed by G. Reinbach, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1898, **3,** p. 309, and L. B. Mendel, Am. J. Physiol., Bost., 1900, **3,** p. 290.

[c] R. Hutchinson, J. Physiol., 1896, **20,** p. 494.

[d] F. Blum, München. med. Wchnschr., 1898, **45,** p. 335.

[e] E. Roos, Ztschr. f. physiol. Chem., Strassb., 1898, **25,** p. 242.

[f] E. Roos, Ztschr. f. physiol. Chem., Strassb., 1899, **28,** p. 40.

[g] F. Blum, Verhandl. des Kong. f. inn. Med., 1906, **23,** p. 196.

to that of thyroid.[a] Since most writers have found either no iodine in the thymus or only traces (in which case it was usually attributed to admixture with thyroid[b]) the conclusion has been drawn that thymus free of iodine has a physiological effect similar to that of thyroid. In reply to this it may be stated that later writers seem to be agreed that thymus has very little activity in goiter. Even granting that thymus does possess a certain degree of activity of a character similar to that of the thyroid, this would not prove that iodine is not a very important constituent of the thyroid. One of the present writers[c] recently showed that there is present in several organs of the body a substance or substances having a physiological action similar, at least in some respects, to that of thyroid, but that the latter, apparently on account of its iodine content, is far more active.

d. Inefficiency of iodothyrine in tetany.—Another argument against the view that the iodine-containing substance (iodothyrine) obtained from the thyroid by Baumann is the active constituent of the thyroid was that it did not prevent tetany in thyroidectomized animals.[d] These experiments were performed before the importance of the parathyroids was recognized and the investigators were endeavoring to control symptoms with which the thyroid had little or nothing to do.

e. Efficiency of iodine compounds other than iodothyrine in goiter.—Baumann argued that iodothyrine was the active principle of the thyroid from the fact that its administration produced the same effects upon certain forms of goiter as did that of the thyroid itself. But attention was called to the fact[e] that a great variety of iodine compounds, both inorganic and organic, had a similar effect in these conditions. Evidently, however, such arguments do not bear directly upon the question whether the iodine is of importance to the thyroid. Recent work indicates that these different forms of iodine are efficient simply because the iodine has a special affinity for the thyroid. The effect of iodine in the treatment of goiter is in reality an argument in favor of the view of the importance of iodine in the thyroid.

A very little consideration suffices to show that none of the above arguments have any very direct bearing upon the problem with which

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[a] J. Mikulicz, Berl. klin. Wchnschr., 1895, **32,** p. 342; G. Reinbach, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1898, **3,** p. 309; R. H. Cunningham, J. Exper. Med., N. Y., 1896, **3,** p. 227.

[b] E. Baumann, München. med. Wchnschr., 1896, **43,** p. 311; R. H. Cunningham, l. c.; H. G. Wells, J. Am. M. Ass., Chicago, 1897, **29,** p. 1009; L. B. Mendel, Am. J. Physiol., Boston, 1900, **3,** p. 285.

[c] R. Hunt, J. Am. M. Ass., Chicago, 1907, **49,** p. 1325.

[d] *cf.* G. von Bunge, Lehrbuch der Physiologie des Menschen, 2 ed., 1905, **2,** p. 632; E. Roos, Ztschr. f. physiol. Chem., Strassb., 1899, **28,** p. 41; 1899, **27,** p. 37.

[e] *cf.* Von Bunge, l. c.

we are concerned, viz, the use of thyroid as a drug. It is not the condition of the thyroid in a living animal which is of interest in this connection. There may be and probably are delicate mechanisms by which the amount and strength of the secretion given off by the thyroid is accurately adjusted to the needs of the body. A gland may be supposed to form a large amount of very active material, but this may not reach the circulation owing to some abnormalities in the blood or lymph vessels or possibly to the absence of some stimulus which normally causes the secretion of the material. In the body the thyroid which has undergone cystic degeneration may be very ineffective in preserving health; but removed from the body and administered as a drug it may have pronounced effects. Similarly we may suppose that in some cases of Grave's disease the thyroid contains normal amounts of active material but that the conditions for the rapid secretion or for the reabsorption of the iodine are so favorable, or that the capacity of the organism to destroy the secretion is lowered, so that there is an accumulation of the active material in the body outside of the thyroid. In such a case there might be a condition of hyperthyroidism, but the gland when administered to an animal as a drug might not be very active. In other words, the effects of a dead organ when administered as a drug can not be compared with the activities of the living organ in the body. Many of the writers who have discussed the relation of iodine to the thyroid have confused these two distinct problems.

If we now turn to the experiments in which the question of the relation of iodine to the thyroid when used as a drug has been approached directly, we find that there is no difference of opinion: all who have worked upon the problem from this standpoint agree as to the importance of the iodine. Unfortunately, however, the experiments of this character are very few and the results are not quantitative.

The experiments bearing on this phase of the subject may be divided into three groups—(*a*) those in which the action of the thyroid upon metabolism, (*b*) upon different forms of goiter, and (*c*) upon the circulation was investigated.

The most important work upon the relation between the iodine content of the thyroid and its effects upon metabolism was done by Roos,[a] who recorded the results of three such experiments upon a dog. In the first experiment the administration of 5 grams of desiccated children's thyroid containing 0.025 per cent iodine had almost no effect upon the excretion of nitrogen or upon body weight; later the administration of 5 grams of children's thyroid containing 0.18 per cent iodine caused an increase in the excretion of nitrogen of about 10 per cent. In the second experiment also a greater effect

[a] E. Roos, Ztschr. f. physiol. Chem., 1899, **28**, p. 40.

was produced by the administration of the thyroid containing the larger percentage of iodine. In the third experiment, in which the dried thyroids of dogs were administered, 5 grams of a preparation containing no iodine had no effect, whereas 5 grams of a preparation which contained 0.35 per cent iodine was followed by a distinct increase in the nitrogen excretion and a slight loss of weight.

Roos's experiments were very few in number and the results not very striking, and perhaps do not justify the very positive conclusions he drew from them.[a] Still they point very distinctly to the conclusion that thyroid rich in iodine has a more marked effect upon nitrogen metabolism than does thyroid poor in, or free of, iodine.

Roos also describes the effects of desiccated hog thyroids containing different percentages of iodine upon four cases of parenchymatous goiter. In all cases thyroid free of iodine had a very slight or doubtful effect, whereas thyroid containing iodine had a marked action in reducing the size of the goiter. In one case the use of doses of 0.5 gram thyroid containing 0.008 per cent iodine had a distinct effect, but the effect of the administration of equal doses of a thyroid containing 0.08 per cent iodine was more marked.

Roos himself recognized that only an approximate estimation of the quantitative effects of thyroid was possible either in metabolism experiments or in the treatment of goiter. He also pointed out the difficulties of drawing any conclusions from observations upon thyroid-ectomized animals, and stated that he deemed it useless to try this method.

Oswald tested the activity of thyreoglobulin containing little iodine upon metabolism, and von Cyon investigated its effects upon the irritability of the vagi.[b] In the two experiments upon metabolism reported by Oswald the thyreoglobulin poor in iodine produced no effect in one case and very slight, if any, in the other; thyreoglobulin rich in iodine produced a marked increase in the nitrogen excretion. Von Cyon reported that thyreoglobulin obtained from colloid goiters and which contained 0.19 per cent iodine had a distinct effect upon the irritability of the vagi, but that this was less than that produced by normal thyroid with a higher percentage of iodine. Von Cyon and Oswald[c] had already found thyreoglobulin free of iodine obtained from goitrous calves to be without any effect upon the circulation. Oswald further states that thyreoglobulin from hog thyroid containing 0.5 per cent iodine seemed more active than that of the human thyroid with 0.3 per cent iodine.[d]

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[a] *cf.* F. Blum, Verhandl. d. Kong. f. inn. Med., 1906, **23,** p. 196.

[b] A. Oswald, Arch. f. path. Anat. [etc.], Berl., 1902, **169,** p. 461; Beitr. z. chem. Physiol. u. Path., Brnschwg., 1902, **2,** p. 555.

[c] E. von Cyon and A. Oswald, Archiv. f. d. ges. Physiol., Bonn, 1901, **83,** p. 202.

[d] A. Oswald, Beitr. z. chem. Physiol. u. Path., Brnschwg., 1902, **2,** p. 556 (footnote).

Marine and Williams[a] have recently reported two experiments on the effects of feeding desiccated sheep thyroid containing different percentages of iodine to dogs. Of one preparation which contained 0.0292 per cent iodine 11 grams fed to a dog in eighteen days did not cause a loss of weight, and the fresh thyroid of the dog on analysis yielded but 0.173 milligram iodine per gram. The second preparation had 0.1092 per cent iodine. The dog which received 11 grams of this in eighteen days lost 454 grams weight and its fresh thyroid contained, per gram, 0.439 milligram iodine.

These experiments, although very few in number and not of a character to admit of quantitative results, indicate clearly that there is a relation between the iodine content and the physiological activity of thyroid preparations.

B. EXPERIMENTAL.

METHODS.

None of the methods discussed in the above review are suitable for a quantitative study of the physiological effects of different thyroid preparations. They are all time-consuming, and so do not admit of many experiments; furthermore, they are not adapted for showing small differences in activity. They did not suffice, for example, to demonstrate the physiological activity of thyroid free of iodine. It may also be mentioned that different animals and different patients may react differently to the same preparation;[b] this has been observed both clinically and experimentally. If it were possible to test the various thyroid preparations upon the same individual fairly concordant results could probably be obtained, but such experiments are, as a rule, not feasible.

Before beginning the description of the method which forms the basis of the experiments described in this bulletin a few words may be said in regard to some observations which we have made upon the relation between the activity of thyroid preparations and the loss in body weight which their ingestion may produce. Many of the results are given in the protocols of the experiments which follow, but in addition to these several experiments were performed expressly for determining whether a method based upon the loss in weight of the animals could be used for estimating the relative activity of

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[a] D. Marine and W. W. Williams, Archives of Internal Medicine, 1908, **1**, p. 378.

[b] The fact that there are such variations in the susceptibility of different individuals can not be considered an argument against the desirability of having thyroid preparations of known strength. It is especially important that when the susceptibility of a patient to a given drug has been determined that treatment should be continued with a preparation of known strength—not with one half or three times as strong, as may readily occur with present commercial thyroid preparations.

thyroid preparations. The figures given in the protocols show the loss of weight for relatively short periods (ten to twenty days) and do not indicate that the method is of practical application. In the special experiments which were undertaken the animals (rats and guinea pigs) were fed during longer periods or until death occurred. The results showed that in general the thyroid with the largest percentage of iodine produced death earliest, but in no case was more than a rough quantitative application of the data possible. It is probable that the primary effect of thyroid feeding is the same in different animals, but that other factors, such as appetite, rate of excretion, etc., which can not be controlled, are involved, and these determine the final result.

The method which we have developed for comparing the physiological activity of different thyroid preparations has for its basis the effect of thyroid feeding upon the resistance of animals to certain poisons. Having found that the administration of thyroid alters the resistance of animals to certain poisons, we performed a large number of experiments in order to determine which poisons were most suitable for comparative studies. The principal poisons tested on mice are included in the following list, and in most cases, as will be seen, negative results were obtained. With many of the compounds in the list but two or three experiments were performed; hence we can not state positively that the feeding of thyroid in these cases had *no* effect upon the resistance to the substance in question. The thyroid, in amounts varying from 0.001 to 0.1 gram per day, was fed in the form of cakes; the poisons were injected subcutaneously:

Acetonecyanhydrine	Resistance slightly increased (?).
Acetonitrile	Resistance much increased.
Acetylmorphine ("Heroin")	Resistance diminished.
Antipyrine	No effect.
Atropine	No effect.
Benzonitrile	No effect.
Butylcarbylamine (tertiary)	No effect.
Caffeine	No effect.
Capronitrile	No effect.
Chloral hydrate	Resistance diminished(?).
Codeine	Resistance diminished.
Ethylcarbylamine	No effect.
Ethylenecyanide	Resistance increased.
Guanidine carbonate	No effect.
Guanidine sulphocyanate	No effect.
Hydrocyanic acid	No effect.
Isovaleraldehydecyanhydrine	No effect.
Methylamine	No effect.
Methylethylketonecyanhydrine	No effect.
Morphine	Resistance diminished.
Nicotine	No effect.

Nitroprussiate of soda	No effect.
Ox gall	No effect.
Phenol	No effect.
Picrotoxin	No effect.
Sodium arsenate	No effect.
Sodium oxalate	No effect.
Strychnine	No effect.
Trimethylenecyanide	Resistance increased.

The poisons to which the resistance of mice was most markedly altered by the feeding of thyroid were acetonitrile and morphine. Since the susceptibility of rats and guinea pigs to these poisons was also changed by the administration of thyroid, they were selected for comparative studies.

The advantages of a method of this kind are that the experiments are quickly and easily carried out and that they admit of the detection of smaller differences in activity than do the methods hitherto employed. It is not possible to state positively that the physiological activity determined in this manner is in all respects a true index of the therapeutic efficiency of the thyroid, but there are many reasons for believing this to be the case. In the first place, thyroid is preeminently a drug that influences metabolism, and the changes in the resistance of animals to the poisons here considered depend upon deep-seated, although little understood, changes in metabolism. In the second place, the results obtained are in complete accord with those observed in clinical studies and with those obtained by other physiological methods. In any case there seems to be much reason for supposing that these reactions are as true an index of the real physiological activity of thyroid as is its effect upon the excretion of urea or upon the circulation.

The experiments were performed upon mice, rats, and guinea pigs. The thyroid was fed to guinea pigs in the form of tablets; to mice and rats in the form of cakes, according to Ehrlich's method. Each cake weighed about 4 grams; mice ate about one cake, rats from one and a half to three cakes per day. The poisons were dissolved in water and injected subcutaneously.

1. EXPERIMENTS WITH ACETONITRILE.

Acetonitrile or methylcyanide, CH_3CN, seems to produce toxic effects chiefly, if not entirely, through the slow liberation in the body of hydrocyanic acid. The views as to the manner in which this formation of hydrocyanic acid takes place have been discussed in a previous bulletin from this laboratory.[a] An additional argument for the view that the toxic effects of acetonitrile are due to the formation

[a] Bulletin 33: Studies in Experimental Alcoholism, 1907, p. 9.

of hydrocyanic acid may perhaps be found in the comparison of the effects of these two poisons upon sulphur metabolism. In the publication referred to above it was stated that under the influence of acetonitrile the "percentage of sulphur excreted as neutral sulphur frequently rose from 25 to 65 or more; the total excretion was not much changed, but the oxidized sulphur frequently almost disappeared." Results very similar to the above have recently been obtained by Richards and Wallace,[a] and by Loewy, Wolf, and Oesterberg[b] with potassium cyanide and hydrocyanic acid.

Richards and Wallace found in one experiment upon a dog poisoned with potassium cyanide that while the total amount of sulphur eliminated remained unchanged the percentage eliminated in the oxidized state was 64.53 on the normal day and 48.78 on the day of poisoning. Loewy, Wolf, and Oesterberg found that in severe poisoning by hydrocyanic acid the sulphur eliminated as neutral sulphur increased from 28.6 per cent to 54.8 per cent. The greater effect upon the sulphur metabolism observed in our experiments was probably due to a more prolonged action of the hydrocyanic acid.

As has been already stated, the administration of thyroid causes marked changes in the susceptibility of animals to acetonitrile. Since thyroid does not alter the resistance of animals (or at least of mice) to hydrocyanic acid,[c] it may be concluded that its action is exerted chiefly upon the processes by which acetonitrile is decomposed in the body and not upon the hydrocyanic acid which is formed from it. In fact, acetonitrile seems to be a very delicate test for detecting changes in metabolism brought about not only by the thyroid and certain other organ products,[d] but by different diets,[e] inanition, etc.

[a] Experiments on Mice.

Preliminary experiments and theoretical considerations.—When small amounts of thyroid are fed to mice for a few days these animals acquire a markedly increased resistance to acetonitrile. This is true not only for white but also for wild gray mice, although most of the experiments were performed upon the former, and unless otherwise stated, white mice are referred to in all of the following experiments.

The following results may be quoted to illustrate from what large amounts of acetonitrile mice which have received small amounts of

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[a] A. N. Richards and G. B. Wallace, J. Biol. Chem., 1908, **4,** p. 179.

[b] A. Loewy, C. G. L. Wolf, and E. Oesterberg, Biochem. Ztschr., 1908, **8,** p. 132.

[c] R. Hunt, J. Biol. Chem., 1906, **1,** p. 42.

[d] J. Am. M. Ass., 1907, **49,** p. 1325.

[e] Proc. Soc. Exper. Biol. and Med., 1906, **3,** p. 15. These results will soon be published in detail.

thyroid may recover. Only those experiments are quoted which show the maximum non-fatal and the minimum fatal dose:

SERIES I.

A. SHEEP THYROID; 0.179 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
February 1	22.62	Feeding of cakes each containing 0.002 gm. thyroid begun.
4	23.02	
7	22.69	
9	23.35	Acetonitrile, 105.08 mgms., i. e., 4.5 mgms. per gm. mouse. Survived.
February 1	22.56	Thyroid as above.
4	22.18	
7	20.62	
10	20.28	Acetonitrile, 93.29 mgm., i. e., 4.6 mgms. per gm. mouse. Died 2 hours.

B. CONTROLS.

1908.		
February 1	18.83	Feeding of cakes without thyroid begun.
4	20.01	
7	20.19	
10	19.02	Acetonitrile, 4.76 mgms., i. e., 0.25 mgm. per gm. mouse. Survived.
February 1	16.49	Cakes as above.
4	15.56	
7	15.79	
10	16.31	Acetonitrile, 4.24 mgms., i. e., 0.26 mgm. per gm. mouse. Died 10 hours.

Summary.—The results of these experiments may be summarized as follows:

	Gm. thyroid fed daily.	Mgm. I in thyroid.	Weight of mouse in gms.	Amount of acetonitrile in mgms.		Result.
				Per mouse.	Per gm. mouse.	
A	0.002	0.0036	23.35	105.08	4.5	Survived.
	.002	.0036	20.28	93.29	4.6	Died.
B	0	0	19.02	4.76	.25	Survived.
	0	0	16.31	4.24	.26	Died.

Thus a mouse (A) which had received thyroid recovered from seventeen times the relative amount of acetonitrile fatal to the control. Since 0.25 mgm. per gram is the maximum amount of the nitrile from which a control (B) recovered, we are justified in assuming that this represents the maximum amount of nitrile which the mice of this series could, under normal conditions, neutralize; for a mouse weighing 23.35 gms. this would be a total of 5.84 mgms. The mouse which weighed 23.35 gms. and which had received thyroid recovered, however, from 105.08 mgms. Hence we may conclude that the thyroid had enabled the mouse to neutralize, or resist in some way, 99.24 mgms. acetonitrile. The mice seldom ate an entire cake (containing 0.002 gm. thyroid) in a day; hence they had received less than 20 mgms. thyroid in all.

SERIES II.

A. DOG THYROID; 0.111 PER CENT IODINE

Date.	Weight of mouse.	Remarks.
1908.		
May 9	15.83	Feeding of cakes each containing 0.0015 gm. thyroid begun.
16	14.05	
18	13.94	Acetonitrile, 64.14 mgms., i. e., 4.6 mgms. per gm. mouse. Survived.

B. CONTROLS.

1908.		
May 9	19.00	Feeding of cakes without thyroid begun.
16	19.86	
18	19.52	Acetonitrile, 5.47 mgms., i. e., 0.28 mgm. per gm. mouse. Died 6 hours.

Summary.—The results of these experiments may be summarized as follows:

	Gm. thyroid fed daily.	Mgm. I in thyroid.	Weight of mouse in gms.	Amount of acetonitrile in mgms.		Result.
				Per mouse.	Per gm. mouse.	
A	0.0015	0.0017	13.94	64.14	4.6	Survived.
B	0	0	19.52	5.47	.28	Died.

The mouse which had received the thyroid recovered from more than sixteen times the relative dose fatal to the controls. A total of less than 15 mgms. of thyroid had led to the physiological neutralization of at least 60.24 mgms. acetonitrile.

SERIES III.

A. SHEEP THYROID; 0.19 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
March 28	15.93	Feeding of cakes each containing 0.001 gm. thyroid begun.
31	14.88	
April 3	15.20	
7	14.33	
8	14.74	Acetonitrile, 67.80 mgms., i. e., 4.6 mgms. per gm. mouse. Survived.
March 28	16.85	Thyroid as above.
31	14.24	
April 3	14.90	
7	14.40	Acetonitrile, 71.12 mgms., i. e., 4.8 mgms. per gm. mouse. Died 1½ hours.

B. CONTROLS.

1908.		
March 28	14.30	Feeding of cakes without thyroid begun.
31	12.88	
April 3	13.15	Acetonitrile, 5.06 mgms., i. e., 0.4 mgm. per gm. mouse. Survived.
7	12.64	
March 28	15.35	Cakes as above.
31	15.06	
April 3	13.17	
7	12.60	
8	12.04	Acetonitrile, 5.06 mgms., i. e., 0.42 mgm. per gm. mouse. Died 1¾ hours.

Summary.—The results of these experiments may be tabulated as follows:

	Gm. thyroid fed daily.	Mgm. I in thyroid.	Weight of mouse in gms.	Amount of acetonitrile in mgms.		Result.
				Per mouse.	Per gm. mouse.	
A	0.001	0.0019	14.74	67.8	4.6	Survived.
	.001	.0019	14.40	71.12	4.8	Died.
B	0	0	12.64	5.06	.4	Survived.
	0	0	12.04	5.06	.42	Died.

The mouse which had received the thyroid recovered from about eleven times the dose fatal to the controls. A total of less than 10 mgms. of thyroid had enabled the mouse to neutralize about 61.8 mgms. acetonitrile.

SERIES IV.

A. SHEEP THYROID; 0.32 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
April 28	18.10	Feeding of cakes, each containing 0.0005 gm. thyroid, begun.
May 2	19.22	
7	18.91	
8	18.91	Acetonitrile, 62.40 mgms., i. e., 3.3 mgms. per gm. mouse. Survived.
April 28	13.48	Thyroid as above.
May 2	14.58	
7	15.03	Acetonitrile, 52.60 mgms., i. e., 3.5 mgms. per gm. mouse. Died 6½ hours.

B. CONTROLS.

1908.		
April 28	18.98	Feeding of cakes without thyroid begun.
May 2	20.34	
7	19.53	
8		Acetonitrile, 10.94 mgms., i. e., 0.56 mgm. per gm. mouse. Survived.
April 28	19.04	Cakes as above.
May 2	20.63	
7	18.83	
8		Acetonitrile, 10.92 mgms., i. e., 0.58 mgm. per gm. mouse. Died 7 hours.

Summary.—The results of these experiments may be tabulated as follows:

	Gm. thyroid fed daily.	Mgm. I in thyroid.	Weight of mouse in gms.	Amount of acetonitrile in mgms.		Result.
				Per mouse.	Per gm. mouse.	
A	0.0005	0.0016	18.91	62.4	3.3	Survived.
	.0005	.0016	15.03	52.6	3.5	Died.
B	0	0	19.53	10.94	.56	Survived.
	0	0	18.83	10.92	.58	Died.

The mouse which had received the thyroid recovered from a dose of acetonitrile about six times as large as that fatal to the controls. Less than 5 mgms. of thyroid had led to the physiological neutralization of about 51.8 mgms. of acetonitrile.

SERIES V.

A. HOG THYROID; 0.33 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1907.		
January 9	19.73	Feeding of cakes, each containing 0.0001 gm. thyroid, begun.
14	19.50	
17	18.82	
19	18.80	Acetonitrile, 18.8 mgms., i. e., 1 mgm. per gm. mouse. Survived.
January 9	13.83	Thyroid as above.
14	15.45	
17	14.47	
19	13.65	
20	13.65	Acetonitrile, 17.75 mgms., i. e., 1.3 mgms. per gm. mouse. Died 2¼ hours.

B. CONTROLS.

1907.		
January 9	16.45	Feeding of cakes without thyroid begun.
14	15.52	
17	15.16	
19	15.07	Acetonitrile, 5.73 mgms., i. e., 0.38 mgm. per gm. mouse. Survived.
January 9	15.25	Cakes as above.
14	15.90	
17	14.70	
19	13.82	
20	13.43	Acetonitrile, 5.51 mgms., i. e., 0.41 mgm. per gm. mouse. Died 5 hours.

Summary.—The results of these experiments may be summarized as follows:

	Gm. thyroid fed daily.	Mgm. I in thyroid.	Weight of mouse in gms.	Amount of acetonitrile in mgms.		Result.
				Per mouse.	Per gm. mouse.	
A	0.0001	0.00033	18.80	18.8	1.0	Survived.
	.0001	.00033	13.65	17.75	1.3	Died.
B	0	0	15.07	5.73	.38	Survived.
	0	0	13.43	5.51	.41	Died.

The mouse which had received thyroid recovered from approximately two and one-half times the dose of acetonitrile fatal to the controls. A total of about 1 mgm. thyroid had enabled the mouse to resist 11.5 mgms. acetonitrile.

We have performed no experiments for the special purpose of determining either the maximum amount of nitrile which may be neutralized under the influence of thyroid or the minimum amount

of thyroid which produces a physiological effect. It is evident, however, from the above that as little as 0.1 mgm. of dry thyroid fed daily for eleven days produced a marked effect; still smaller amounts would doubtlessly have produced a distinct effect.

As was shown in a previous paper,[a] this reaction of mice is a very delicate test for thyroid. A few milligrams of thyroid mixed with a large amount of blood or of toasted bread, tamarinds, liquorice powder, etc. (as in the case of a number of the secret "antifat" nostrums), may readily be detected. We have found no other substance with an effect upon the resistance of mice to acetonitrile at all comparable to that of thyroid. This physiological test for thyroid is far more delicate than any chemical method for its detection.[b]

In most of our experiments the thyroid was fed for nine or ten days before the injection of the nitrile. This period was selected in part arbitrarily and in part because we were convinced that it was sufficiently long for the maximum effect of the thyroid to have been produced. A very distinct effect was, however, present in a much shorter time; thus mice which had received rather large amounts of an active thyroid preparation for but two days recovered after the injection of twice the dose of nitrile fatal to the controls.

We have few data as to how long the effect of the thyroid continues after the feeding is discontinued. We have observed in some cases, however, that the increased resistance persisted, although it was less, for at least two weeks.

Conditions influencing the resistance of mice to acetonitrile.—Different groups of mice vary in their susceptibility to acetonitrile; hence in carrying out a series of experiments with this substance it is absolutely indispensable to have mice which have been kept under uniform conditions. In testing the effect of thyroid it is also necessary to have a number of controls for each series of experiments. With these precautions we have rarely failed to obtain entirely concordant results and have as a rule determined the fatal dose of the nitrile

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[a] R. Hunt, J. Am. M. Ass., 1907, **49,** p. 240.

[b] As was pointed out in the paper referred to above, this method seemed adapted to throw some light on the question whether there is an excessive amount of thyroid secretion in the blood in cases of Grave's disease. So far we have been able to test the blood in only three such cases. In one of these the blood had a marked effect in increasing the resistance of mice to acetonitrile, indicating an excessive amount of thyroid secretion. In another case the results were doubtful; the amount of blood was insufficient for even two experiments. In the third case the results were negative. Possibly this test may have some diagnostic value, although on the thyroid theory of Grave's disease it is not necessary to assume that an excess of thyroid secretion is present in the blood at all times. So far as our observations go it is probable that the best results would be obtained by administering 1 or 2 c. c. of the blood to mice daily for nine or ten days before testing with the nitrile. Several controls (mice fed with normal blood) are indispensable.

to within 0.01 mgm. per gram body weight. The protocols of the experiments described later show what satisfactory results may, with careful work, be obtained.

It has not been possible to determine all the causes of the differences in susceptibility of different groups of mice to acetonitrile. Diet seems, however, to be the most important single factor; mice kept on certain diets for long periods may be many times as resistant as others of the same age and weight kept on a different diet.

Another very important factor in the toxicity is the season. We have records of experiments performed in each month for three and in some cases for four years. Although the diet was approximately the same throughout the year, the mice were invariably more susceptible to the acetonitrile during the summer than during the winter months. The following table shows the average fatal dose (in milligrams per gram) determined during different months:

January	0.56	May	0.30	September	0.25
February	.35	June	.28	October	.39
March	.58	July	.31	November	.45
April	.53	August	.18	December	.55

There were greater variations (in different series of experiments) in the winter than in the summer months, but in only three cases were the figures as low as the average for the summer months. During the winter months the mice were kept in a room heated to 75° F. (23.9° C.); hence it is not probable that the temperature was the only factor.[a]

On the manner in which thyroid influences the resistance of mice to acetonitrile.—We are unable to suggest any entirely satisfactory explanation of how the feeding of thyroid protects mice against

[a] D. W. Harrington (Am. J. Physiol., 1898, **1,** p. 385) has recorded some very interesting experiments on the relation of season to the susceptibility of the guinea pig to anesthetics and operative procedures; the resistance was very low from February to May and highest from October to January. Stimulation of the vagus was more effective in stopping the heart during the fall and winter than during the spring months. Prof. C. W. Edmunds, of the University of Michigan, found frogs to be much less resistant to digitalis in April than during the summer months.

The following statement of F. C. Koch (Proc. Am. Pharm. Ass., 1907, **55,** p. 371) is very interesting in this connection: "I have recently had occasion to determine the per cent of iodine in unadulterated desiccated sheep thyroids prepared at different seasons during the last two and one-half years, and found that the desiccations without exception test as much as three times higher during the winter months than during June and July, and that the per cent gradually diminished toward the summer months and then again gradually increased toward the winter."

Although it is very probable that the differences found by Koch depend upon differences in diet, it is remarkable that the time of the minimum amount of iodine in sheep thyroid should coincide with the period of least resistance of mice to acetonitrile; as we shall see later the resistance of animals to acetonitrile is closely dependent upon the amount of iodine which their thyroids contain.

acetonitrile. The effect is the reverse of the one which was anticipated from certain theoretical considerations and which led us to perform the experiments. Inasmuch as the view that one of the functions of the thyroid is to neutralize poisons is very widely held and, since the "neutralization" (or rendering harmless) of acetonitrile in the mouse under the influence of thyroid is the only instance[a] in which a poison is apparently neutralized in any animal—all the other "poisons" to which reference is so frequently made are purely hypothetical—a few words may be devoted to this subject. In the first place, there is certainly no reason to suppose that there is any direct chemical neutralization of the acetonitrile by the thyroid—an interpretation which some have placed upon our previously published results. Not only is it impossible to think of any way in which such a neutralization could occur, but the amounts of the nitrile which may be rendered harmless are so out of proportion to the amounts of thyroid fed that any such interaction is highly improbable. It was shown in the experiments quoted above that from 1 to 20 mgm. of thyroid fed during the course of nine or ten days enabled mice to resist the toxic effects of from five to ten times an equal weight of acetonitrile. By far the greater part of the thyroid is doubtlessly made up of physiologically inert material; hence the disproportion between the amount of poison "neutralized" and the "neutralizing" agent is still greater. It is interesting to compare in this respect the effect of a very active substance—iodothyrine—derived from the thyroid.

Experiment, February 10, 1908: The iodothyrine used in this experiment was a commercial preparation (Baeyer) stated to contain 1 part of iodothyrine mixed with 309 parts of milk sugar;[b] it contained 0.014 per cent iodine.

A. IODOTHYRINE (BAEYER).

Date.	Weight of mouse.	Remarks.
1908.		
February 1....	19.43	Feeding of cakes each containing 0.005 gm. iodothyrine begun.
4....	18.60	
8....	17.55	
9....	17.30	Acetonitrile, 43.25 mgms., i. e., 2.5 mgms. per gm. mouse. Survived.
February 1....	20.40	Iodothyrine as above.
4....	19.76	
8....	19.70	
10....	19.07	Acetonitrile, 49.58 mgms., i. e., 2.6 mgms. per gm. mouse. Died 1 hour.

[a] With the exception of two nitriles closely related to acetonitrile (see p. 20–1).

[b] See New and Non-Official Remedies, 3d ed., 1908, p. 74.

B. CONTROLS.

Date.	Weight of mouse.	Remarks.
1908.		
February 1....	18.83	Feeding of cakes without iodothyrine.
4....	20.01	
7....	20.19	
10....	19.02	Acetonitrile, 4.76 mgms., i. e., 0.25 mgm. per gm. mouse. Survived.
February 1....	16.49	Cakes as above.
4....	15.56	
7....	15.79	
10....	16.31	Acetonitrile, 4.24 mgms., i. e., 0.26 mgm. per gm. mouse. Died 10 hours.

Summary.—0.005 gm. of the milk sugar trituration was fed; this mixture contained only 1 part of the true iodothyrine in 310. Hence there was fed daily but 0.0161 mgm. iodothyrine. The results are summarized in the following table:

	Mgm. true iodothyrine fed daily.	Mgm. I in true iodothyrine.	Weight of mouse in gms.	Amount of acetonitrile in mgms.		Result.
				Per mouse.	Per gm. mouse.	
A	0.0161	0.00000225	17.30	43.25	2.5	Recovered.
	.0161	.00000225	19.07	49.58	2.6	Died.
B	0	0	19.02	4.76	.25	Recovered.
	0	0	16.31	4.24	.26	Died.

Thus a mouse (A) which had received iodothyrine recovered from nearly ten times the relative amount of acetonitrile fatal to the controls. Since 0.25 mgm. per gram is the maximum amount of acetonitrile from which a control (B) recovered, we are justified in assuming that this represents the maximum amount of the poison which a mouse of this series could, under normal conditions, neutralize; for a mouse weighing 17.30 gms. (A) this would be a total of 4.33 mgms. The mouse which weighed 17.30 gms. and which had received iodothyrine recovered, however, from 43.25 mgms. Hence we may conclude that the iodothyrine had enabled the mouse to resist in some way the poisonous effects of 38.92 mgms. acetonitrile. The total amount of iodothyrine which the mouse had received in ten days was somewhat less than 0.161 mgm. Thus one part of true iodothyrine fed to a mouse in the course of ten days had enabled it to resist more than 240 times an equal weight of acetonitrile.

Although we speak of the poison being "neutralized" when a mouse, as a result of the administration of thyroid, recovers from several times the fatal dose of acetonitrile, it is very probable that there has been no neutralization whatever. The effect is probably a preventive one—that is, the thyroid in some way prevents the formation of a poison from the nitrile. The basis of this suggestion is the fact that the feeding of thyroid has no effect upon the toxicity of

hydrocyanic acid itself, the poison produced from the nitrile.[a] The thyroid seems to alter the metabolism in such a way that the acetonitrile is disposed of without its breaking down into poisonous constituents, as occurs in the normal animal.[b] Were there a direct interaction between the poison and the thyroid the same results would be expected in all classes of animals; but as we shall see, thyroid not only does not protect rats and guinea pigs against acetonitrile, but it increases their susceptibility to this poison.

The activity of the thyroid in relation to acetonitrile is in sharp contrast to that of certain sulphur compounds. The latter are true antidotes for acetonitrile as well as for many other cyanogen compounds.[c] The hydrocyanic acid which is formed from these compounds as well as hydrocyanic acid administered as such is neutralized by sulphur with the formation of sulphocyanate; the latter compound is less toxic to warm-blooded animals than the cyanogen compounds themselves. The action of the sulphur compounds is the same in all classes of animals investigated.

An hypothesis similar to that which was advanced above to explain the manner in which the feeding of thyroid increases the resistance of mice to acetonitrile—that the thyroid simply alters metabolic processes in such a way that a poisonous substance is not produced from the nitrile—seems sufficient to explain what is frequently called the detoxicatory action of the thyroid. In the normal organism the thyroid probably has a directing influence upon metabolism of such a character that all the products of metabolism are converted into useful or at least harmless compounds. In the absence of the thyroid the metabolism probably proceeds along abnormal lines, with the result that substances necessary for the proper functioning of certain organs are not formed; possibly poisonous substances are also produced, although the evidence is against this supposition.[d] This hypothesis seems more reasonable than one assuming that poisonous substances are normally produced and that an organ has been evolved for the purpose of neutralizing them.

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[a] This argument is, of course, by no means conclusive. It is possible that after the feeding of thyroid hydrocyanic acid is produced from the nitrile, but in such a manner or in a place where it can be neutralized by the body, whereas when hydrocyanic acid itself is administered it may not reach the cells or parts of cells where neutralization is possible. A study of the sulphocyanate excretion of thyroid fed mice after the administration of acetonitrile might throw some light on this subject.

[b] Another possibility which may be considered in this connection is that mice may, under the influence of thyroid, utilize acetonitrile for the synthesis of protein or other nitrogen-containing bodies. Latham (Biochem. J., 1908, **3,** p. 193) believes that certain nitriles are utilized in this way in the normal animal.

[c] See R. Hunt, Arch. internat. de pharmacodyn. e. d. ther., 1904, **12,** p. 447.

[d] The blood of thyroidectomized animals is not, according to a number of writers, toxic; *cf.* L. Launoy, Semaine méd., Par., 1908, **28,** p. 382; D. Baldi, Arch. ital. de biol., Turin, 1899, **31,** p. 281.

It seems unnecessary to divide the functions of the thyroid into "metabolic" and "detoxicatory," as is sometimes done. It is sufficient to recognize that the thyroid has certain effects—for the most part unknown—upon metabolism. Under normal conditions these effects lead to the formation of useful substances or promote in other ways cellular activities. When an unusual poison, such as acetonitrile, is introduced into an animal under the influence of thyroid, its fate will depend upon how the animal's metabolism as regards this poison has been affected by the thyroid; the latter alters the metabolism of the mouse in such a way that the acetonitrile is rendered harmless or is prevented from becoming harmful, but it alters the metabolic processes of rats and guinea pigs in such a way that the acetonitrile becomes much more harmful. In a somewhat similar way certain processes of oxidation proceed along definite lines; for instance, when a poison such as ethyl alcohol is introduced into the body these processes of oxidation destroy it, thus not only making it harmless, but the body is enabled to utilize the energy set free. In the case of methyl alcohol, however, although the oxidation may proceed along similar lines, part of the alcohol is converted into substances (formaldehyde and formic acid) more poisonous than the original substance. The fate of acetonitrile in the body of a mouse to which thyroid has been administered may be compared to the fate of ethyl alcohol; that of acetonitrile in the body of a rat which has received thyroid to that of methyl alcohol.

i. EXPERIMENTS WITH "IODINE FREE" THYROID.[a]

The question whether thyroid free of iodine has any physiological activity has, like the entire question of the relation of iodine to the thyroid, been approached from two points of view. Those who have considered it from the standpoint of the activity of a living gland in

[a] By "iodine free" thyroid we mean thyroid which does not give even a qualitative test for iodine when 1 gm. of sample is examined by the Baumann method. The limit of this method when applied to a complex body like the thyroid, which contains a very large amount of organic matter, is about 0.01 per cent; although somewhat smaller amounts of iodine could be satisfactorily estimated by using more than 1 gm. of material. As is well known, Paul Bourcet (Compt. rend. Acad. d. sc., Par. 1899, **128,** p. 1120) modified the Baumann method so that very much smaller amounts of iodine could be determined when 50 to 1,000 gms. of the material were employed. The modification consists in concentrating the solution of the fused mass obtained by the incineration of the sample and removing the potassium sulphate by repeated precipitation with alcohol. By this method Bourcet was able to estimate as small an amount as 0.1 mgm. of iodine per kilogram of sample. A. R. Dochez (Johns Hopkins Hospital Bull. 1908, **19,** p. 235) using this method, found iodine in crystallized cane sugar, egg yolk, "C. P. glucose," and in a very large number of other ordinary foods. Of the substances examined only C. P. lactose, egg albumen, chocolate, almonds, and pig embryos (thyroids excised) were reported as containing no iodine.

It is very probable that the thyroid which we call "iodine free" would have been found to contain iodine if examined by Bourcet's modification, and it is also possible

the body have assumed that such thyroid is active (Neumeister, Miwa and Stoeltzner, Hutchinson). Those, on the other hand, who have studied the question from the pharmacological side, i. e., in the same way as other drugs are studied, have denied that such thyroid has any physiological activity (Roos, Oswald, Von Cyon and Oswald).

One of the present writers[a] stated in a preliminary paper that he had found thyroid free of iodine to have a low degree of physiological activity. The experiments upon which this statement was based will now be described in detail.

The thyroid most frequently used in these experiments was obtained from infants who had died of various diseases. About 80 such glands were dried at 50° to 60° C., powdered, and thoroughly mixed. There were also available small amounts of thyroid from Maltese kids, an Alaskan bear, and an aoudad.[b] None of these preparations, when examined by the usual method for detecting iodine in the thyroid, gave even a qualitative test for this element.[c]

That the thyroids of children usually contain little or no iodine was first pointed out by Baumann.[d] This investigator found that the presence or absence of iodine and the amount of the latter, when present, varied according to the locality from which the glands were obtained. Nine of twelve thyroids of infants under $1\frac{1}{2}$ years of age, from Freiburg, contained no iodine; three contained from 0.007 to 0.015 per cent. Of six infants from Berlin $1\frac{1}{2}$ years or less of age the thyroids of five contained from 0.014 to 0.033 per cent of iodine; those of the sixth contained none. The thyroids of six children from Hamburg had an average iodine content of 0.07 per cent.

Miwa and Stöltzner[e] examined the thyroids of twelve infants from Berlin; in but one was iodine found, and then only to the extent of 0.025 per cent. Weiss[f] examined the thyroids of seven children under $4\frac{1}{4}$ years; the iodine varied from traces to 0.037 per cent.

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that these traces of iodine are responsible for the physiological effects we attribute to "iodine free" thyroid. On the other hand, if these thyroids were found to contain traces of iodine it does not follow that this iodine was in the form of combination peculiar to the thyroid.

[a] R. Hunt, J. Am. M. Ass., Chicago, 1907, **49,** 1324.

[b] We are much indebted to Dr. J. R. Mohler, Chief of the Division of Pathology, Bureau of Animal Industry, Department of Agriculture, and pathologist to the National Zoological Park, for the thyroids of these and of a number of other rare animals. The children's thyroids were obtained from Baltimore. In this connection it may be mentioned that H. G. Wells (J. Am. M. Ass., 1897, **29,** p. 1011) found the average percentage of iodine in the thyroid of six adults of Baltimore to be 0.236.

[c] Two gms. of the children's thyroids, 1 of the Maltese kids, 1 of the Alaskan bear, and 0.3 of the aoudad were used for the tests.

[d] E. Baumann, Ztschr. f. physiol. Chem., Strassb., 1896, **22,** p. 11.

[e] S. Miwa and W. Stöltzner, Jahrb. f. Kinderh., 1897, **45,** p. 87.

[f] F. Weiss, München. med. Wchnschr., 1897, **44,** p. 6.

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Wells [a] analyzed the thyroids of six children from Chicago under 4 years; three had but traces, the other three from 0.011 to 0.092 per cent. Von Rositzky [b] reported analyses of the thyroids of eight children under 10 years of age; the percentage of iodine varied from 0.012 to 0.041. Oswald [c] found in five children from Basel under 7 years from traces to 0.061 per cent iodine. Charrin and Bourcet [d] found in the thyroid of infants under 3 months who were born of healthy mothers from 0.0004 to 0.0054 per cent iodine. In many cases in which the child or mother had suffered from various diseases no iodine was found. Mendel [e] found no iodine in the thyroids of four infants; that of a fifth contained 0.07 mgm. Jolin [f] found in twenty-seven infants in Sweden under 4 years no distinct traces of iodine in seven cases and from traces to 0.086 per cent in the others. Nagel and Roos [g] found no iodine in the thyroids of four new-born puppies.

The following experiments were performed with the iodine free preparations described above. A few experiments with thyroid containing various amounts of iodine are quoted for comparison. In all cases the dried and powdered gland was used.

SERIES I.

A. THYROID OF CHILDREN; FREE OF IODINE.

Date.	Weight of mouse.	Remarks.
1906.		
February 24....	22.06	Feeding of cakes each containing 0.05 gm. thyroid begun.
March 3.....	22.85	
6.....	22.15	Acetonitrile, 17.72 mgms., i. e., 0.8 mgm. per gm. mouse. Survived.
7.....	.....	Acetonitrile, 26.58 mgms., i. e., 1.2 mgms. per gm. mouse. Survived.
February 24....	17.22	Thyroid as above.
March 3.....	18.05	
6.....	17.75	Acetonitrile, 17.75 mgms., i. e., 1 mgm. per gm. mouse. Survived.
7.....	.....	Acetonitrile, 24.85 mgms., i. e., 1.4 mgms. per gm. mouse. Survived.

B. CONTROLS.

1906.		
February 21....	20.75	Cakes without thyroid.
March 3.....	19.85	
6.....	18.75	Acetonitrile, 5.63 mgm., i. e., 0.3 mgm. per gm. mouse. Died 2 hours.
February 21....	22.71	Cakes without thyroid.
March 3.....	22.55	
6.....	20.95	Acetonitrile, 7.33 mgms., i. e., 0.35 mgm. per gm. mouse. Died 1 to 3 hours.
February 21....	23.71	Cakes without thyroid.
March 3.....	25.35	
6.....	24.45	Acetonitrile, 12.23 mgms., i. e., 0.5 mgm. per gm. mouse. Died 1 hour.

[a] H. G. Wells, J. Am. M. Ass., Chicago, 1897, **29**, p. 955.
[b] A. v. Rositzky, Wien. klin. Wchnschr., 1897, **37**, p. 823.
[c] A. Oswald, Ztschr. f. physiol. Chem., Strassb., 1897, **23**, p. 291.
[d] A. Charrin and P. Bourcet, Compt. rend. Acad. d. sc., Par. 1900, **130**, p. 945.
[e] L. B. Mendel, Am. J. Physiol., Boston, 1900, **3**, p. 287.
[f] S. Jolin, Festschrift O. Hammarsten, Upsala, 1906.
[g] W. A. Nagel and E. Roos, Arch. f. (Anat. u.) Physiol., Suppl. Bd., 1902, p. 275.

Summary.—The results of the above experiments may be summarized as follows:

Thyroid.	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Fatal dose of acetonitrile in mgms. per gm.	
			Recovered.	Died.
A. Children's	0.05	0	1.4	
B. Controls				0.3

Unfortunately the experiments were not sufficiently numerous for the fatal doses to be determined, but it is evident that the children's thyroid had protected the mice against at least five times the dose of acetonitrile fatal to the controls.

Series II.

A. CHILDREN'S THYROID; IODINE FREE.

Date.	Weight of mouse.	Remarks.
1906.		
July 28	20.51	Feeding of cakes each containing 0.05 gm. thyroid begun.
30	20.40	
August 3	19.00	
7	16.80	
9	15.69	Acetonitrile, 31.38 mgms., i. e., 2 mgms. per gm. mouse. Survived.
July 28	21.63	Thyroid as above.
30	20.96	
August 3	21.00	
7	19.00	
9	18.50	
10	18.50	Acetonitrile, 38.85 mgms., i. e., 2.1 mgms. per gm. mouse. Died 1½ hours.

B. SHEEP THYROID; 0.176 PER CENT IODINE.

1906.		
July 28	23.71	Feeding of cakes each containing 0.05 gm. thyroid begun.
30	22.79	
August 3	20.39	
7	17.91	Acetonitrile, 25.07 mgms., i. e., 1.4 mgms. per gm. mouse. Survived.
July 28	24.52	Thyroid as above.
30	21.14	
August 3	19.00	
7	15.70	
8	15.25	Acetonitrile, 30.5 mgms., i. e., 2 mgms. per gm. mouse. Survived.
July 28	15.81	Thyroid as above.
30	16.53	
August 3	16.56	
7	17.50	
9	14.33	Acetonitrile, 32.96 mgms., i. e., 2.3 mgms. per gm. mouse. Died 1¾ hours.
July 28	14.11	Thyroid as above.
30	14.36	
August 3	14.08	
4	12.78	
9	12.41	Acetonitrile, 32.27 mgms., i. e., 2.6 mgms. per gm. mouse. Died 2 hours.

C. CONTROLS.

Date.	Weight of mouse.	Remarks.	
1906.			
July 28	22.42	Cakes without thyroid	
30	23.51		
August 3	24.70		
7	22.83		
8	21.91	Acetonitrile, 3.07 mgms., i. e., 0.14 mgm. per gm. mouse.	Survived.
July 28	27.68	Cakes without thyroid.	
30	28.02		
August 3	28.73		
7	27.04		
9	24.61	Acetonitrile, 4.18 mgms., i. e., 0.17 mgm. per gm. mouse.	Survived.
July 28	22.33	Cakes without thyroid.	
30	21.62		
August 3	21.11		
7	18.42		
8	17.58	Acetonitrile, 3.52 mgms., i. e., 0.20 mgm. per gm. mouse.	Died 1 to 2 hours.
July 28	21.85	Cakes without thyroid.	
30	22.30		
August 3	22.06		
7	20.77	Acetonitrile, 5.19 mgms., i. e., 0.25 mgm. per gm. mouse.	Died $1\frac{3}{4}$ hours.

Summary.—The results of the above experiments may be summarized as follows:

Thyroid.	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A. Children's	0.05	0	0	2.0	2.1
B. Sheep	.05	.176	.088	2.0	2.3
C. Controls				.17	.2

In these experiments both the children's and sheep's thyroids protected against ten times the fatal dose of acetonitrile; the iodine free children's thyroids were as effective as the iodine containing sheep's thyroids. But, as appears from the following experiments, too much thyroid had been given to admit of comparison—that is, the maximum effect had been produced in each case.

In the next series smaller amounts of children's thyroid were fed and the results compared with those obtained with guinea pig's thyroid; the latter contained 0.05 per cent iodine.

Series III.

A. CHILDREN'S THYROID; IODINE FREE.

Date.	Weight of mouse.	Remarks.
1907.		
April 5	23.33	Feeding of cakes each containing 0.02 gm. thyroid begun.
8	22.66	
11	21.42	
15	19.92	Acetonitrile, 9.96 mgms., i. e., 0.5 mgm. per gm. mouse. Survived.
April 5	23.35	Thyroids as above.
8	23.31	
11	23.95	
15	24.22	
16	23.82	Acetonitrile, 14.29 mgms., i. e., 0.6 mgm. per gm. mouse. Died 2 hours.
April 5	26.50	Thyroid as above.
8	26.46	
11	25.35	
14	24.32	Acetonitrile, 17.02 mgms., i. e., 0.7 mgm. per gm. mouse. Died about 9 hours.

B. GUINEA PIG THYROID; 0.05 PER CENT IODINE.

1907.		
April 5	.....	Feeding of cakes each containing 0.0035 gm. thyroid commenced.
8	14.65	
11	16.02	
15	15.62	Acetonitrile, 9.37 mgms., i. e., 0.6 mgm. per gm. mouse. Survived.
April 5	.....	Thyroid as above.
8	18.72	
11	18.68	
15	17.50	
16	17.82	Acetonitrile, 14.26 mgms., i. e., 0.8 mgm. per gm. mouse. Survived.
April 5	.....	Thyroid as above.
8	17.85	
11	18.27	
15	18.60	Acetonitrile, 18.60 mgms., i. e., 1 mgm. per gm. mouse. Died 3⅓ hours.

C. CONTROLS.

1907.		
April 5	23.01	Cakes without thyroid.
8	21.85	
11	22.42	
15	22.52	Acetonitrile, 6.76 mgms., i. e., 0.3 mgm. per gm. mouse. Survived.
April 5	18.06	Cakes as above.
8	15.32	
11	15.32	
15	14.90	
16	15.45	Acetonitrile, 5.41 mgms., i. e., 0.35 mgm. per gm. mouse. Died 2½ hours.
April 5	18.01	Cakes as above.
8	15.36	
11	16.00	
14	15.40	Acetonitrile, 6.16 mgms., i. e., 0.4 mgm. per gm. mouse. Died about 11¾ hours.

Summary.—The results of the above experiments may be summarized as follows:

Thyroid.	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed.	Fatal dose acetonitrile in mgm. per gm. mouse.	
				Recovered.	Died.
A. Children	0.02	0	0	0.5	0.6
B. Guinea pig	.0035	.05	.0017	.8	1.0
C. Controls				.3	.35

Thus the mice which had received the guinea pig thyroid (B) recovered from about one and five-tenths times the dose of acetonitrile fatal to the mice which had received the children's thyroid (A). Five and seven-tenths times as much of the children's thyroid as of the guinea pig's thyroid had been fed; hence we may conclude that the latter was approximately eight and five-tenths times as active as the former.

Series IV.

A. THYROID OF MALTESE KID;[a] NO IODINE.

Date.	Weight of mouse.	Remarks.
1907.		
April 27	12.33	Feeding of cakes each containing 0.05 gm. thyroid begun
30	12.67	
May 3	12.65	
4	12.50	Acetonitrile, 8.75 mgms., i. e., 0.7 mgm. per gm. mouse. Survived.
April 27	20.93	Thyroid as above.
30	19.82	
May 3	20.82	
4	21.67	
7	21.73	
10	22.71	
14	22.95	Acetonitrile, 20.66 mgms., i. e., 0.9 mgm. per gm. mouse. Died 2 hours.
April 27	22.53	Thyroid as above.
30	19.51	
May 3	21.87	
4	22.42	
7	22.61	
10	22.91	
13	22.85	Acetonitrile, 27.42 mgms., i. e., 1.2 mgms per gm. mouse. Died 4 hours.

[a] Unfortunately no microscopic examination was made of these glands. They weighed 17.65 gms. fresh; 3.25 gms. dry. Thus more than 81.5 per cent consisted of water. They were apparently abnormal (glandular hyperplasia?).

B. CHILDREN'S THYROID; IODINE FREE.

Date.	Weight of mouse.	Remarks.
1907.		
April 27	11.90	Feeding of cakes each containing 0.05 gm. thyroid begun.
30	12.55	
May 3	12.76	
4	12.27	Acetonitrile, 8.59 mgms., i. e., 0.7 mgm. per gm. mouse. Survived.
April 27	15.01	Thyroid as above.
30	15.15	
May 3	15.45	
4	15.58	
7	15.67	
10	15.21	
13	14.39	Acetonitrile, 14.39 mgms., i. e., 1 mgm. per gm. mouse. Survived.
April 27	20.11	Thyroid as above.
30	19.27	
May 3	18.60	
4	18.25	
7	18.17	
10	17.71	
14	15.83	Acetonitrile, 18.99 mgms., i. e., 1.2 mgms. per gm. mouse. Survived.

C. GUINEA PIG THYROID; 0.05 PER CENT IODINE.

1907.		
April 27	13.73	Feeding of cakes each containing 0.007 gm. thyroid begun.
30	13.00	
May 3	12.42	
4	12.80	Acetonitrile, 10.24 mgms., i. e., 0.8 mgm. per gm. mouse. Survived.
April 27	12.65	Thyroid as above.
30	13.42	
May 3	13.32	
7	12.76	
10	12.01	
13	11.47	Acetonitrile, 11.47 mgms., i. e., 1 mgm. per gm. mouse. Survived.
April 27	17.12	Thyroid as above.
30	17.40	
May 3	17.12	
4	16.25	
7	15.61	
10	15.83	
13	15.20	Acetonitrile, 22.80 mgms., i. e., 1.5 mgms. per gm. mouse. Survived.
April 27	24.35	Thyroid as above.
30	24.83	
May 3	24.32	
4	24.06	
7	24.56	
10	24.53	
14	24.67	Acetonitrile, 49.34 mgms., i. e., 2 mgms. per gm. mouse. Survived.

D. CONTROLS.

Date.	Weight of mouse.	Remarks.
1907.		
April 27	13.63	Cakes without thyroid.
May 3	13.95	
4	13.52	Acetonitrile, 3.38 mgms., i. e., 0.25 mgm. per gm. mouse. Survived.
April 27	15.62	Cakes as above.
30	16.65	
May 3	15.43	
7	14.91	
10	14.35	
14	14.02	Acetonitrile, 3.93 mgms., i. e., 0.28 mgm. per gm. mouse. Died 2½ hours.
April 27	13.12	Cakes as above.
30	13.07	
May 3	12.33	
4	12.02	
7	11.45	
10	11.55	
13	11.25	Acetonitrile, 3.94 mgms., i. e., 0.35 mgm. per gm. mouse. Died 7 hours.
April 27	20.57	Cakes as above.
30	21.40	
May 3	20.00	
4	20.32	Acetonitrile, 10.16 mgms., i. e., 0.5 mgm. per gm. mouse. Died 10 hours.

Summary.—These results may be tabulated as follows:

Thyroid.	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mg. I in thyroid fed.	Fatal dose of acetonitrile in mgms. per gm. mouse.	
				Recovered.	Died.
A. Maltese kid	0.05	0	0	0.7	0.9
B. Children	.05	0	0	1.2	.....
C. Guinea pig	.007	.05	.0035	2.0	.....
D. Controls	.....	.....	.....	.25	.28

Unfortunately the experiments were not sufficiently numerous to permit of a determination of the fatal dose in all cases. The guinea pig thyroid (C) protected against more than twice as much acetonitrile as did the thyroid of the Maltese kid (A); since seven times as much of the latter as of the former was given, we may consider that the guinea pig thyroid is more than fourteen times as active as that of the Maltese kid. Another point of interest in this series is that the children's thyroid (B) was more active than the Maltese kid thyroid; this shows that there are differences in activity of different "iodine free" thyroids.

Owing to lack of material but few experiments were made with smaller amounts of children's thyroid and the results were not altogether satisfactory; 1 mgm. fed daily for ten days had slight, if any, effect.

Series V.

A. THYROID OF ALASKAN BEAR; IODINE FREE.

Date.	Weight of mouse.	Remarks.
1908.		
May 19	16.54	Feeding of cakes each containing 0.005 gm. thyroid begun.
23	15.49	
27	15.25	Acetonitrile, 6.87 mgms., i. e., 0.45 mgm. per gm. mouse. Survived.
May 19	11.83	Thyroid as above.
23	11.35	
27	10.13	
28	.....	Acetonitrile, 4.86 mgms., i. e., 0.48 mgm. per gm. mouse. Survived.
May 19	16.75	Thyroid as above.
23	16.77	
27	16.23	Acetonitrile, 8.44 mgms., i. e., 0.52 mgm. per gm. mouse. Died 2½ hours.
May 19	17.43	Thyroid as above.
23	16.66	
27	16.33	Acetonitrile, 9.80 mgms., i. e., 0.60 mgm. per gm. mouse. Died 1½ hours.

B. THYROID OF AOUDAD; IODINE FREE.

1908.		
May 19	15.39	Feeding of cakes each containing 0.005 gm. thyroid begun.
23	17.03	
27	16.00	
28	.....	Acetonitrile, 6.40 mgms., i. e., 0.40 mgm. per gm. mouse. Died 1½ hours.
May 19	15.87	Thyroid as above.
23	15.73	
27	14.65	Acetonitrile, 7.62 mgms., i. e., 0.52 mgm. per gm. mouse. Died 2½ hours
May 19	15.07	Thyroid as above.
23	14.30	
27	13.50	Acetonitrile, 8.10 mgms., i. e., 0.60 mgm. per gm. mouse. Died 2 hours.

C. THYROID OF BLACK LEOPARD; 0.01 PER CENT IODINE.

1908.		
May 19	19.12	Feeding of cakes, each containing 0.005 gm. thyroid begun.
23	18.15	
27	18.99	
28	.....	Acetonitrile, 9.50 mgms., i. e., 0.50 mgm. per gm. mouse. Died 1¼ hours.
May 19	18.03	Thyroid as above.
23	17.32	
27	16.65	Acetonitrile, 11.66 mgms., i. e., 0.70 mgm. per gm. mouse. Died 2¼ hours.
May 19	19.04	Thyroid as above.
23	18.78	
27	18.56	Acetonitrile, 16.70 mgms., i. e., 0.90 mgm. per gm. mouse. Died 3 hours.

D. THYRADEN;[a] 0.085 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
May 19	15.50	Feeding of cakes each containing 0.00125 gm. thyraden begun.
23	14.81	
27	13.12	Acetonitrile, 9.18 mgms., i. e., 0.7 mgm. per gm. mouse. Survived.
May 19	18.46	Thyroid as above.
23	17.30	
28	16.23	Acetonitrile, 12 98 mgms., i. e., 0.8 mgm. per gm. mouse. Survived.
May 19	15.19	Thyroid as above.
23	15.03	
27	14.65	Acetonitrile, 13.19 mgms., i. e., 0.9 mgm. per gm. mouse. Died 1 hour.
May 19	16.69	Thyroid as above.
23	14.53	
27	14.02	Acetonitrile, 14.02 mgms., i. e., 1 mgm. per gm. mouse. Died 1¼ hours.

[a] This is a commercial lactose trituration of dried thyroid claimed to be standardized to contain 0.07 per cent iodine. Two specimens examined by us were found to contain slightly more iodine than this, viz, 0.085 per cent.

E. CONTROLS.

1908.		
May 19	15.79	Feeding of cakes without thyroid begun.
23	15.65	
27	15.87	Acetonitrile, 3.97 mgms., i. e., 0.25 mgm. per gm. mouse. Survived.
May 19	15.66	Cakes as above.
23	15.24	
27	16.02	
28	.....	Acetonitrile, 4.17 mgms., i. e., 0.26 mgm. per gm. mouse. Died 4¾ hours.
May 19	17.55	Cakes as above.
23	18.15	
26	18.10	Acetonitrile, 5.43 mgms., i. e., 0.30 mgm. per gm. mouse. Died 2 hours.
May 19	11.80	Cakes as above.
23	11.70	
27	10.34	Acetonitrile, 3.31 mgms., i. e., 0.32 mgm. per gm. mouse. Died 3 hours.

Summary.—The results of the above experiments may be summarized as follows:

Thyroid.	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed.	Fatal dose of acetonitrile in mgm. per gm. mouse.	
				Recovered.	Died.
A. Alaskan bear	0.005	0	0	0.48	0.52
B. Aoudad	.005	0	0	.....	.40
C Black leopard	.005	.01	.0001	.....	.50
D. Thyraden	.00125	.085	.0011	.80	.90
E. Controls	.....	.....	.....	.25	.26

The iodine free thyroid of the Alaskan bear (A) had some physiological activity, but it was much (perhaps about seven times) less than that of Thyraden (D), with 0.085 per cent iodine. The iodine free thyroid of the aoudad (B) was evidently less active than that of the Alaskan bear; in fact, there is nothing in this series to indicate that it had any activity whatever, but perhaps the doses of acetonitrile were too large. A point of interest is the fact that the thyroid of the black leopard (C), which contained 0.01 per cent iodine, was certainly not more active than the "iodine free" thyroid of the Alaskan bear. Of course it is possible that there was a small amount of iodine in the latter which was overlooked in the analysis; unless this is the case (and the probabilities are that it is not) we must conclude that at times iodine free thyroid is as active as thyroid containing a minimum amount of iodine.

SERIES VI.

A. THYROID OF MALTESE KID; IODINE FREE.

Date.	Weight of mouse.	Remarks.
1908.		
September 5...	17.60	Feeding of cakes each containing 0.01 gm. thyroid commenced.
9...	17.24	
12...	16.90	
14...	16.02	Acetonitrile, 4 mgms., i. e., 0.25 mgm. per gm. mouse. Survived.
September 5...	18.76	Thyroid as above.
9...	18.02	
12...	17.72	
14...	17.13	Acetonitrile, 4.62 mgms., i. e., 0.27 mgm. per gm. mouse. Died 2 hours.
September 5...	18.75	Thyroid as above.
9...	19.70	
12...	19.54	
13...	.....	Acetonitrile, 5.86 mgms., i. e., 0.3 mgm. per gm. mouse. Died 2½ hours.
September 5...	19.40	Thyroid as above.
9...	17.30	
12...	17.04	
13...	.....	Acetonitrile, 7.67 mgms., i. e., 0.45 mgm. per gm. mouse. Died 1½ hours.

B. THYROID OF ALASKAN BEAR; IODINE FREE.

1908.		
September 5...	17.40	Feeding of cakes each containing 0.01 gm. thyroid commenced.
9...	17.82	
12...	18.88	
14...	19.02	Acetonitrile, 8.56 mgms., i. e., 0.45 mgm. per gm. mouse. Survived.
September 5...	15.24	Thyroid as above.
9...	14.46	
12...	14.80	
13...	.....	Acetonitrile, 7.4 mgms., i. e., 0.5 mgm. per gm. mouse. Survived.
September 5...	20.24	Thyroid as above.
9...	20.08	
12...	19.28	
14...	18.94	Acetonitrile, 10.04 mgms., i. e., 0.53 mgm. per gm. mouse. Died 1½ hours.
September 5...	19.00	Thyroid as above.
9...	18.76	
12...	18.00	
13...	.....	Acetonitrile, 10.8 mgms., i. e., 0.6 mgm. per gm. mouse. Died 3 hours.

C. THYROID OF CHILDREN; IODINE FREE.

Date.	Weight of mouse.	Remarks.
1908.		
September 5...	19.88	Feeding of cakes each containing 0.01 gm. thyroid commenced.
9...	20.92	
12...	19.94	
13...	.....	Acetonitrile, 8.97 mgms., i. e., 0.45 mgm. per gm. mouse. Survived.
September 5...	14.84	Thyroid as above.
9...	16.20	
12...	16.26	
14...	15.95	Acetonitrile, 8.45 mgms., i. e., 0.53 mgm. per gm. mouse. Survived.
September 5...	17.06	Thyroid as above.
9...	15.80	
12...	16.00	
14...	15.13	Acetonitrile, 8.62 mgms., i. e., 0.57 mgm. per gm. mouse. Died 1½ hours.
September 5...	15.68	Thyroid as above.
9...	14.42	
12...	14.24	
13...	.....	Acetonitrile, 8.54 mgms., i. e., 0.6 mgm. per gm. mouse. Died 8 hours.

D. THYROID OF BLACK LEOPARD; 0.01 PER CENT IODINE.

1908.		
September 5...	17.14	Feeding of cakes each containing 0.01 gm. thyroid commenced.
9...	18.10	
12...	17.68	
14...	17.23	Acetonitrile, 4.31 mgms., i. e., 0.25 mgm. per gm. mouse. Survived.
September 5...	18.08	Thyroid as above.
9...	18.22	
12...	18.18	
14...	17.85	Acetonitrile, 4.82 mgms., i. e., 0.27 mgm. per gm. mouse. Survived.
September 5...	19.00	Thyroid as above.
9...	19.52	
12...	19.24	
13...	.....	Acetonitrile, 5.77 mgms., i. e., 0.3 mgm. per gm. mouse. Died 2½ hours.
September 5...	17.08	Thyroid as above.
9...	16.92	
12...	16.78	
13..	.....	Acetonitrile, 7.55 mgms., i. e., 0.45 mgm. per gm. mouse. Died 2 hours.

E. THYROID OF SHEEP; 0.125 PER CENT IODINE.

1908.		
September 5...	18.56	Feeding of cakes each containing 0.001 gm. thyroid commenced.
9...	19.16	
12...	18.54	
13...	.....	Acetonitrile, 27.81 mgms., i. e., 1.5 mgms. per gm. mouse. Survived.
September 5...	19.52	Thyroid as above.
9...	19.98	
12...	18.16	
14...	19.25	Acetonitrile, 30.8 mgms., i. e., 1.6 mgms. per gm. mouse. Survived.
September 5...	21.44	Thyroid as above.
9...	19.00	
12...	18.52	
13...	.....	Acetonitrile, 31.48 mgms., i. e., 1.7 mgms. per gm. mouse. Died 1 hour.
September 5...	18.00	Thyroid as above.
9...	18.43	
12...	18.24	
14...	16.98	Acetonitrile, 30.56 mgms., i. e., 1.8 mgms. per gm. mouse. Died 2¾ hours.

F. CONTROLS.

Date.	Weight of mouse.	Remarks.
1908.		
September 5...	18.04	Feeding of cakes without thyroid commenced.
9...	17.50	
12...	17.20	
14...	17.00	Acetonitrile, 1.87 mgms., i. e., 0.11 mgm. per gm. mouse. Survived.
September 5...	19.78	Cakes as above.
9...	20.50	
12...	20.56	
14...	20.29	Acetonitrile, 2.64 mgms., i. e., 0.13 mgm. per gm. mouse. Died 2½ hours.
September 5...	21.14	Cakes as above.
9...	20.52	
12...	20.48	
14...	20.22	Acetonitrile, 3.03 mgms., i. e., 0.15 mgm. per gm. mouse. Died 3 hours.
September 5...	21.32	Cakes as above.
9...	22.16	
12...	22.40	
13...	.....	Acetonitrile, 4.03 mgms., i. e., 0.18 mgm. per gm. mouse. Died 5 hours.

SUMMARY.

Thyroid.	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A. Maltese kid	0.01	0	0	0.25	0.27
B. Alaskan bear	.01	0	0	.50	.53
C. Children	.01	0	0	.53	.57
D. Black leopard	.01	.01	.001	.27	.30
E. Sheep	.001	.125	.00125	1.60	1.70
F. Controls				.11	.13

The three iodine free thyroids (A, B, and C) protected mice against more than twice the dose of acetonitrile fatal to the controls; those of the Alaskan bear and of children were about twice as active as that of the Maltese kid. The thyroid of the black leopard, although it contained a small percentage of iodine, was only about half as active as the thyroids of the Alaskan bear and of the children. One one-thousandth of a gram of sheep thyroid, containing 0.125 per cent iodine, protected against about three times as much acetonitrile as did ten times as much of the iodine free children's thyroid; we may therefore conclude that it was about thirty times as active as the latter.

Series VII.

A. THYROID OF ALASKAN BEAR; IODINE FREE.

Date.	Weight of mouse.	Remarks.
1908.		
June 1	17.06	Feeding of cakes each containing 0.01 gm. thyroid begun.
5	15.45	
9	15.00	
10	.....	Acetonitrile, 3.90 mgms., i. e., 0.26 mgm. per gm. mouse. Survived.
June 1	17.50	Thyroid as above.
5	15.28	
9	15.68	
11	16.32	Acetonitrile, 5.06 mgms., i. e., 0.31 mgm. per gm. mouse. Survived.
June 1	13.50	Thyroid as above.
5	14.02	
9	13.50	Acetonitrile, 5.40 mgms., i. e., 0.40 mgm. per gm. mouse. Died 1¼ hours.
June 1	16.74	Thyroid as above.
5	16.95	
9	17.02	Acetonitrile, 9.36 mgms., i. e., 0.55 mgm. per gm. mouse. Died 4 hours.

B. THYROID OF AOUDAD; IODINE FREE.

1908.		
June 1	18.94	Feeding of cakes each containing 0.01 gm. thyroid begun.
5	18.52	
9	16.52	
10	.....	Acetonitrile, 3.63 mgms., i. e., 0.22 mgm. per gm. mouse. Died 2 hours.
June 1	24.32	Thyroid as above.
5	23.39	
9	23.46	
10	.....	Acetonitrile, 6.57 mgms., i. e., 0.28 mgm. per gm mouse. Died 1½ hours.
June 1	17.17	Thyroid as above.
5	16.86	
9	16.66	Acetonitrile, 8.33 mgms., i. e., 0.50 mgm. per gm. mouse. Died 1¼ hours.

C. THYROID OF BLACK LEOPARD; 0.01 PER CENT IODINE.

1908.		
June 1	15.54	Feeding of cakes each containing 0.01 gm. thyroid begun.
5	14.70	
9	15.14	Acetonitrile, 5.30 mgms., i. e., 0.35 mgm. per gm. mouse. Survived.
June 1	16.72	Thyroid as above.
5	15.07	
9	13.18	
10	.....	Acetonitrile, 5.27 mgms., i. e., 0.40 mgm. per gm. mouse. Died 2¾ hours.
June 1	17.44	Thyroid as above.
5	16.07	
9	15.87	
10	.....	Acetonitrile, 7.14 mgms., i. e., 0.45 mgm. per gm mouse. Died 2¾ hours.
June 1	19.12	Thyroid as above.
5	17.72	
9	18.33	Acetonitrile, 10.08 mgms., i. e., 0.55 mgm. per gm. mouse. Died 1¾ hours.

D. THYROID OF CAT; 0.08 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
June 1	16.56	Feeding of cakes each containing 0.001 gm. thyroid begun.
5	15.05	
9	14.00	Acetonitrile, 7 mgms., i e., 0.5 mgm. per gm. mouse. Survived.
June 1	14.08	Thyroid as above.
5	14.34	
9	14.44	Acetronitrile, 10.11 mgm., i. e., 0.7 mgm. per gm. mouse. Survived.
June 1	19.29	Thyroid as above.
5	18.34	
9	17.86	
10	.....	Acetonitrile, 15.18 mgms., i e., 0.85 mgm. per gm. mouse. Died 1½ hours.
June 1	17.29	Thyroid as above.
5	16.50	
9	15.68	
10	.....	Acetonitrile, 15.68 mgms., i. e., 1 mgm. per gm. mouse. Died 2 hours.

E. THYRADEN; 0.085 PER CENT IODINE.

1908.		
June 1	14.18	Feeding of cakes each containing 0.001 gm. thyraden begun.
5	12.25	
9	11.88	Acetronitrile, 8.39 mgms., i. e., 0.7 mgm. per gm. mouse. Survived.
June 1	17.04	Thyraden as above.
5	16.22	
9	14.78	Acetonitrile, 11.23 mgms., i. e., 0.76 mgm. per gm. mouse. Survived.
June 1	16.02	Thyraden as above.
5	15.56	
9	15.94	
10	.....	Acetonitrile, 13.55 mgms., i. e., 0.85 mgm. per gm. mouse. Died 3¼ hours.
June 1	24.70	Thyraden as above.
5	23.58	
9	22.50	Acetronitrile, 22.50 mgms., i. e., 1 mgm. per gm. mouse. Died 4 hours.

F. THYROID OF DEER; 0.193 PER CENT IODINE.

1908.		
June 1	18.82	Feeding of cakes each conta ning 0.001 gm. thyroid begun.
5	17.70	
9	16.60	Acetonitrile, 8.30 mgms., i. e., 0.5 mgm. per gm. mouse. Survived.
June 1	16.16	Thyroid as above.
5	14.50	
9	15.30	Acetonitrile, 10.71 mgms., i. e., 0.7 mgm. per gm. mouse. Survived.
June 1	16.34	Thyroid as above.
5	14.60	
9	15.14	
10	.....	Acetonitrile, 13.63 mgms., i. e., 0.9 mgm. per gm. mouse. Survived.
June 1	17.67	Thyroid as above.
5	15.30	
9	15.54	
10	.....	Acetonitrile, 20.20 mgms., i. e., 1.3 mgms., per gm. mouse. Survived.

G. CONTROLS.

Date.	Weight of mouse.	Remarks.
1908.		
June 1	15.38	Feeding of cakes without thyroid begun.
5	15.10	
9	13.92	Acetonitrile, 2.09 mgms., i. e., 0.15 mgm. per gm. mouse. Survived.
June 1	16.14	Cakes as above.
5	15.42	
9	15.30	
11	15.92	Acetonitrile, 2.55 mgms., i. e., 0.16 mgm. per gm. mouse. Survived.
June 1	16.42	Cakes as above.
5	16.86	
9	15.72	
10	.....	Acetonitrile, 2.67 mgms., i. e., 0.17 mgm. per gm. mouse. Survived.
June 1	23.34	Cakes as above.
5	21.88	
9	21.45	
10	.....	Acetonitrile, 3.86 mgms., i. e., 0.18 mgm. per gm. mouse. Died 1 hour.
June 1	17.02	Cakes as above.
5	16.00	
9	14.78	
10	.....	Acetonitrile, 2.81 mgms., i. e., 0.19 mgm. per gm. mouse. Died 4½ hours.
June 1	18.30	Cakes as above.
5	18.42	
9	17.66	Acetonitrile, 3.53 mgms., i. e., 0.20 mgm. per gm. mouse. Died 1¾ hours.

Summary.—The results of the above experiments may be tabuated as follows:

Thyroid.	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of acetonitrile in mgm. per gm. mouse.	
				Recovered.	Died.
A. Alaskan bear	0.01	0	0	0.31	0.40
B. Aoudad	.01	0	0	.....	.22
C. Black leopard	.01	.01	.001	.35	.40
D. Cat	.001	.08	.0008	.70	.85
E. Thyraden	.001	.085	.00085	.76	.85
F. Deer	.001	.193	.00193	1.30	.....
G. Controls	.....	.....	.....	.17	.18

The thyroid of the Alaskan bear (A) had a low degree of physiological activity. Inasmuch as 0.01 gm. (per cake) protected against only about one-half as much acetonitrile as did 0.001 of thyraden (0.085 per cent iodine), we may estimate the physiological activity of the latter to be approximately twenty times as great at that of the former. If the aoudad thyroid (B) had any physiological activity, it was too slight to be demonstrated by these experiments; in any case, it was distinctly weaker than the Alaskan bear thyroid (A). The thyroid of the black leopard (C) with 0.01 per cent iodine was apparently no more active than the iodine free thyroid of the Alaskan

bear. The experiments with the cat (D) and deer (F) thyroids show that there is a direct parallelism between the iodine content and the physiological activity of thyroid.

SUMMARY AND GENERAL CONCLUSIONS.

The above experiments show that iodine free thyroid, or what is usually called "iodine free" thyroid, has, when tested by our method, a low degree of physiological activity; this result is contrary to that reported by others. The experiments also show that the activity of such thyroid is much less than that of thyroid containing more than distinct traces (0.01 per cent, for example) of iodine. It is also evident that there are differences in the activity of different "iodine free" thyroids; those of the Alaskan bear and of children were more active than those of the Maltese kid or of the aoudad. This may be explained on either of two suppositions: it may be assumed that the activity of the so-called "iodine free" thyroid is in reality due to iodine which is present in too small amounts to be detected when only small samples are available for analysis and that there is more iodine in the thyroids of the children and of the Alaskan bear than in those of the Maltese kid and of the aoudad. Or we may suppose that the iodine free thyreoglobulin has of itself some activity and that the greater activity of some of the "iodine free" thyroids is due to their containing a larger amount of this thyreoglobublin than do other thyroids. This suggestion would also explain why certain "iodine free" thyroids (children and Alaskan bear) are more active than thyroid (black leopard) containing a minimum amount of iodine. The effect of a large amount of iodine free thyreoglobulin may be greater than that of a small amount of iodine containing thyreoglobulin. In connection with this suggestion attention may be called to the work of Oswald,[a] in which it is shown that the thyreoglobulin varies greatly in amount in different thyroids.

Evidence will be presented in later parts of this bulletin that the physiological activity of the thyroid increases in direct proportion to the amount of iodine contained in proper combination. Some of the bearings (upon the physiology and pathology of the thyroid) of this view that iodine free thyroid has a certain degree of activity and that this is much increased by the presence, in proper combination, of iodine have been discussed by one of the present writers in a previous paper.[b] Another application of this conception may be referred to, although it is not our purpose to discuss fully in this connection these collateral subjects. It was stated in the historical review (p. 13) that one of the arguments advanced against the view

[a] A. Oswald, Beitr. z. chem. Physiol. u. Path., Brnschwg., 1902, **2**, p. 545.

[b] R. Hunt, J. Am. M. Ass., Chicago, 1907, **49**, p. 1325.

that iodine (or rather an iodine containing substance) is an important constituent of the thyroid was the fact that the removal of thyroids which contain no iodine is followed by as severe symptoms as the removal of those which do contain iodine. Such a result would be inexplicable on the view that an iodine compound is an essential constituent of the thyroid; it would, however, be intelligible on the hypothesis that thyroid free of iodine alone has a certain degree of physiological activity. We may suppose that this iodine free or iodine poor thyreoglobulin is sufficient, as a rule, for the ordinary purposes of the organism. Much of the iodine usually found in the thyroid may be considered as one of those "factors of safety" discussed by Meltzer.[a] That the iodine free or iodine poor thyreoglobulin is not, however, always adequate to meet the demands of the body is shown, for example, by the losses suffered by sheep breeders on account of cretin lambs before the extensive use of iodine containing salt.[b]

Another indication that the iodine serves a useful purpose is that there is in general an inverse ratio between the size of the thyroid and the amount of iodine it contains.

ii. COMPARATIVE PHYSIOLOGICAL ACTIVITY OF COMMERCIAL SHEEP THYROIDS.

Inasmuch as most of the commercial thyroid preparations are obtained from the sheep, and as these are official in the United States and several other pharmacopœias, especial attention was given to the comparison of their iodine content and physiological activity. There is a widespread belief among clinicians that commercial thyroid preparations differ considerably in activity; we believe that this opinion is fully justified.

Before describing the results of our experiments a few remarks may be made as to the character of quantitative results which may be expected in a study of the physiological action of drugs. When the great importance, both theoretical and practical, of dosage in medicine is considered, it is remarkable that so little work has been done on the scientific principles underlying it.[c] Not many physicians would assume that by doubling the dose of a drug twice the effect would be produced, yet the relation between successive increments of the dose and the physiological effects is unknown in the case of nearly all drugs. With some drugs, in certain doses, double the amount will produce twice the physiological effect. In other

[a] S. J. Meltzer, J. Am. M. Ass., Chicago, 1907, **48,** p. 655.

[b] *cf.* D. Marine, Johns Hopkins Hosp. Bull., 1907, **18,** p. 359.

[c] *cf.* Juckuff, Versuche zur Auffindung eines Dosierungsgesetztes, Leipzig, 1895; E. Harnack, München med. Wchnschr., 1896, **43,** p. 1065; J. T. Cash, Brit. Med. J., Lond., 1908, i, p. 1213.

doses an increase of 10 per cent in the amount may produce twice the effect. With still other doses the amount administered may be increased many times before twice the effect is produced.

The relation between the percentage of iodine in thyroid and its activity in increasing the resistance of mice to acetonitrile seems to offer an unusually favorable opportunity for a study of this character, but we have not been able to devote special attention to it. A brief discussion of the subject is, however, indispensable for an understanding of our results and the conclusions we draw from them. From the experiments already described (Series II, children's thyroids, p. 35) it is evident that even a very weak thyroid preparation will, when given in a sufficient dose, produce as great a physiological effect as an equal amount of a very active preparation. In other words, there is a limit to the degree of resistance which the body can acquire even under the most favorable circumstances. It is obviously necessary, in comparing the physiological effects of different thyroid preparations, to avoid doses which produce a maximum effect. Also, as the doses approach the maximum, each successive increase produces a relatively smaller effect. A curve expressing these facts graphically is a parabola; at a certain point a preparation with twice the activity of another will produce twice the effect; one with three times the activity would produce three times the effect, etc. The farther removed the doses are from this optimum the less close is the correspondence between the size of the dose of the preparation and its (measurable) physiological effect. The range through which there is a direct relation between the physiological activity of the thyroid and the amount of acetonitrile which may be rendered harmless under its influence seems to be rather great; this doubtlessly accounts for the comparative ease with which we have obtained quantitative results in the following experiments.

In work of this character it is not only permissible but necessary to exclude experiments in which the thyroid produced maximum effects. Thus it would obviously be unwarranted to conclude from the experiments of Series II (p. 35) that the thyroid of children is as active as that of sheep because 0.05 gm. of the former protected against as much acetonitrile as did 0.05 gm. of the latter; in each case the amount fed was probably far above that necessary to produce the maximum effect.

The plan of our experiments was as follows: When the activity of several thyroid preparations was to be compared, they were fed in equal amounts, but care was taken that the quantities administered were such as we believed would produce submaximum effects. It was sometimes necessary to perform two or three series of experiments of this character before the amounts most suitable for comparison could be determined; this was partly due to the fact that

different lots of mice reacted differently. Thus with some mice 0.001 gm. each of several thyroid preparations produced a maximum effect; in such a case it was necessary to repeat the experiments using 0.0005 gm. for example. In other cases the physiological effects produced by the feeding of 0.001 gm. of different thyroid preparations were very slight; in such cases the experiments were repeated with 0.002 or more gram. When the experiments were performed in this manner we found that the amount of acetonitrile from which the mice recovered under the influence of the thyroid was almost directly proportional to the amount of iodine the thyroid contained; hence we conclude that the physiological activity of thyroid is proportional to the iodine content. The correctness of this conclusion was often confirmed as follows: If it required twice as much acetonitrile to cause the death of mice to which thyroid A had been fed as of those to which an equal amount of thyroid B had been fed, we found that the fatal dose of the nitrile was about the same in each case when two parts of B on the one hand and one part of A on the other were fed.[a] Results of greater scientific accuracy could probably have been obtained by a slightly different method of experimenting. Thus instead of comparing the total amount of thyroid which produced a given degree of protection, it would probably have been more accurate to first subtract the "maximum ineffective" dose (i. e., the maximum amount of thyroid which could be fed without producing any demonstrable physiological effect) [b] and comparing only the amounts in excess of this dose. Similarly it would have probably been more accurate to subtract from the maximum nonlethal doses of the nitrile the maximum doses from which the mice would have recovered had they received no thyroid. In this way the amounts of the poison actually neutralized under the influence of the thyroid would have been compared. Such refinements of experimentation were, however, not necessary for our purpose, which was simply to determine if there is a parallelism between the iodine content and the physiological activity of the thyroid

It may be well to emphasize again some of the precautions necessary in this work. One of the most important of these is to have mice which have been kept under uniform conditions; the susceptibility of different lots of mice may vary widely even at the same season. Hence it is necessary to have a number of controls for each series of experiments. It is also necessary to work with doses which are not too near either the minimum or the maximum

[a] This method of double control is similar to the one adopted by one of us in comparing the physiological activity of suprarenal preparations. (J. Am. M. Ass., 1906, **47**, p. 790.)

[b] *cf.* J. T. Cash, Brit. M. J., Lond., 1908, i, p. 1213.

Great care is also required in making the cakes. In some of our experiments we have worked with 1 part of thyroid mixed with 40,000 parts of cracker dust. It is obvious that a uniform distribution of such a small amount of thyroid in such a large amount of cracker dust by ordinary laboratory methods requires considerable care. That, however, remarkably concordant results may be obtained by this method is sufficiently demonstrated by the experiments which follow.

SERIES I.

A. SHEEP THYROID; 0.087 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1907.		
November 22...	22.63	Feeding of cakes each containing 0.005 gm. thyroid commenced.
26...	22.45	
29...	21.62	
December 2...	21.52	Acetonitrile, 38.74 mgms., i. e., 1.8 mgms. per gm. mouse. Survived.
November 22...	16.32	Thyroid as above.
26...	16.42	
29...	16.59	
December 2...	16.07	
3...	16.32	Acetonitrile, 32.64 mgms., i. e., 2 mgms. per gm. mouse. Died 1½ hours.
November 22...	20.39	Thyroid as above.
26...	19.44	
29...	19.10	
December 2...	18.59	
3...	18.87	Acetonitrile, 41.5 mgms., i. e., 2.2 mgms. per gm. mouse. Died 2 hours.
November 22...	21.79	Thyroid as above.
26...	21.57	
29...	20.70	
December 2...	19.63	
3...	18.26	Acetonitrile, 45.65 mgms., i. e., 2.5 mgms. per gm. mouse. Died 1 hour.

B. SHEEP THYROID; 0.17 PER CENT IODINE.

1907.		
November 22...	18.52	Feeding of cakes each containing 0.005 gm. thyroid begun.
26...	18.35	
29...	18.33	
December 2...	17.04	Acetonitrile, 34.1 mgms., i. e., 2 mgms. per gm. mouse. Survived.
November 22...	22.92	Thyroid as above.
26...	21.00	
29...	21.65	
December 2...	20.64	Acetonitrile, 57.79 mgms., i. e., 2.8 mgms. per gm. mouse. Survived.
November 22...	16.00	Thyroid as above.
26...	16.39	
29...	16.56	
December 2...	16.70	
3...	15.74	Acetonitrile, 55.09 mgms., i. e., 3.5 mgms. per gm. mouse. Survived.
November 22...	20.28	Thyroid as above.
26...	18.41	
29...	18.35	
December 2...	17.48	
3...	17.08	Acetonitrile, 78.3 mgms., i. e., 4 mgms. per gm. mouse. Died ¾ hour.

C. CONTROLS.

Date.	Weight of mouse.	Remarks.
1907.		
November 22...	20.03	Feeding of cakes without thyroid begun.
26...	20.17	
29...	19.85	
December 2...	19.30	Acetonitrile, 7.33 mgms., i. e., 0.38 mgm. per gm. mouse. Survived.
November 22...	21.38	Cakes as above.
26...	20.00	
29...	20.26	
December 2...	19.07	
3...	18.86	Acetonitrile, 8.11 mgms., i. e., 0.43 mgm. per gm. mouse. Survived.
November 22...	22.67	Cakes as above.
26...	20.40	
29...	19.44	
December 2...	19.30	Acetonitrile, 8.69 mgms., i. e., 0.45 mgm. per gm. mouse. Died 4 hours.
November 22...	23.63	Cakes as above.
26...	22.89	
29...	21.65	
December 2...	21.96	
3...	22.32	
4...	22.43	Acetonitrile, 10.54 mgms., i. e., 0.47 mgm. per gm. mouse. Died 2 hours.

Summary.—The results of the above experiments may be summarized as follows:

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.005	0.087	0.00435	1.8	2.0
B	.005	.170	.0085	3.5	4.0
C. Controls				.43	.45

The thyroid with approximately twice the amount of iodine protected against approximately twice the dose of acetonitrile.

SERIES II.

The same thyroid preparations as above were used, but twice as much of the iodine poor as of the iodine rich was given. The experiments were performed upon a different lot of mice.

A. SHEEP THYROID; 0.17 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1907.		
December 5...	16.00	Feeding of cakes each containing 0.002 gm. thyroid begun.
9...	15.67	
12...	16.28	
14...	15.72	
15...	15.80	Acetonitrile, 33.18 mgms., i. e., 2.1 mgms. per gm. mouse. Survived.
December 5...	17.54	Thyroid as above.
9...	18.06	
12...	18.13	
14...	17.91	
15...	17.57	Acetonitrile, 40.41 mgms., i. e., 2.3 mgms. per gm. mouse. Survived.
December 5...	20.08	Thyroid as above.
9...	21.20	
12...	20.92	
14...	20.65	Acetonitrile, 49.56 mgms., i. e., 2.4 mgms. per gm. mouse. Died 2 to 3 hours.
December 5...	15.37	Thyroid as above.
9...	15.16	
12...	15.36	
14...	16.31	Acetonitrile, 48.93 mgms., i. e., 3 mgms. per gm. mouse. Died $5\frac{3}{4}$ hours.

B. SHEEP THYROID; 0.087 PER CENT IODINE.

1907.		
December 5...	14.00	Feeding of cakes each containing 0.004 gm. thyroid begun.
9...	14.92	
12...	14.42	
14...	14.76	
15...	14.05	Acetonitrile, 28.1 mgms., i. e., 2 mgms. per gm. mouse. Survived.
December 5...	15.17	Thyroid as above.
9...	15.49	
12...	15.37	
14...	15.22	
15...	14.28	Acetonitrile, 32.84 mgms., i. e., 2.3 mgms. per gm. mouse. Survived.
December 5...	16.41	Thyroid as above.
9...	16.59	
12...	16.46	
14...	16.54	
15...	16.30	Acetonitrile, 40.75 mgms., i. e., 2.5 mgms. per gm. mouse. Died 2 hours.
December 5...	19.38	Thyroid as above.
9...	20.86	
12...	21.76	
14...	21.46	Acetonitrile, 60.09 mgms., i. e., 2.8 mgms. per gm. mouse. Died $3\frac{1}{2}$ hours.

C. CONTROLS.[a]

Date.	Weight of mouse.	Remarks.
1907.		
December 5...	17.55	Feeding of cakes without thyroid begun.
9...	17.38	
12...	17.54	
14...	17.93	
15...	17.80	Acetonitrile, 3.03 mgms., i. e., 0.17 mgm. per gm. mouse. Survived.
December 5...	15.33	Cakes as above.
9...	15.88	
12...	16.25	
14...	16.52	
15...	15.97	Acetonitrile, 3.03 mgms., i. e., 0.19 mgm. per gm. mouse. Died 1½ hours.
December 5...	17.31	Cakes as above.
9...	17.91	
12...	17.53	
14...	18.12	Acetonitrile, 3.81 mgms., i. e., 0.21 mgm. per gm. mouse. Died 2½ hours.
December 5...	15.09	Cakes as above.
9...	15.24	
12...	14.85	
14...	15.06	Acetonitrile, 3.77 mgms., i. e., 0.25 mgm. per gm. mouse. Died 6½ hours.

[a] It will be noticed that the fatal dose of acetonitrile for the mice of this series was less than one-half as large as that for those of the preceding series. Such variations in susceptibility are frequent and are largely the result of diet, differences in age, weight, etc.; it illustrates the necessity for using only those mice which have been kept under identical conditions and also the necessity for many controls.

Summary.—The results of the above experiments may be summarized as follows:

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.004	0.087	0.00348	2.3	2.5
B	.002	.17	.0034	2.3	2.4
C. Controls				.17	.19

When two parts of A (0.087 per cent iodine) and one part of B (0.17 per cent iodine) were fed, equal physiological effects were produced.

SERIES III.

In this series both of the methods referred to above were employed, i. e., equal amounts of thyroid containing different amounts of iodine and different amounts of thyroid containing equal amounts of iodine were given. Unfortunately we are not absolutely certain that the analytical data are entirely correct for one of the preparations, viz, that stated to contain 0.061 per cent of iodine. This was the figure obtained on the analysis of a sample taken from the surface of the bottle; later analyses of the thoroughly mixed contents of the bottle showed 0.1 per cent iodine. Inasmuch as the physiological activity of the surface layer corresponded to that of thyroid

containing about 0.061 per cent iodine, and as we have often found that the percentage of iodine in a sample of thyroid can be fairly accurately determined by these physiological tests, we are inclined to believe the analysis correct. Even supposing that the thyroid used contained 0.1 per cent iodine, the results show that there is at least a general parallelism between the iodine content and the physiological activity of the thyroid.

A. SHEEP THYROID; 0.061 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1907.		
November 28...	15.97	Feeding of cakes, each containing 0.002 gm. thyroid, commenced.
30...	15.66	
December 3...	15.45	
6...	15.36	
7...	15.25	Acetonitrile, 13.73 mgms., i. e., 0.9 mgm. per gm. mouse. Survived.
November 28...	18.04	Thyroid as above.
30...	17.82	
December 3...	17.63	
6...	17.19	
8...	17.36	Acetonitrile, 19.1 mgms., i. e., 1.1 mgms. per gm. mouse. Survived.
November 28...	19.99	Thyroid as above.
30...	20.39	
December 3...	21.38	
6...	20.59	
7...	20.64	Acetonitrile, 24.77 mgms., i. e., 1.2 mgms. per gm. mouse. Died, 3 hours.
November 28...	18.89	Thyroid as above.
30...	18.08	
December 3...	17.93	
6...	17.52	
8...	17.88	Acetonitrile, 23.24 mgms., i. e., 1.3 mgms. per gm. mouse. Died, 1 hour.

B. SHEEP THYROID; 0.061 PER CENT IODINE.

1907.		
November 28...	16.32	Feeding of cakes, each containing 0.006 gm. thyroid, commenced.
30...	16.24	
December 3...	15.77	
6...	15.52	
7...	15.72	Acetonitrile, 23.58 mgms., i. e., 1.5 mgms. per gm. mouse. Survived.
November 28...	15.06	Thyroid as above.
30...	13.35	
December 3...	13.50	
6...	13.23	
7...	13.60	Acetonitrile, 32.64 mgms., i. e., 2.4 mgms. per gm. mouse. Survived.
November 28...	17.62	Thyroid as above.
30...	17.46	
December 3...	18.06	
6...	17.78	
8...	19.05	Acetonitrile, 59.06 mgms., i. e., 3.1 mgms. per gm. mouse. Survived.
November 28...	21.43	Thyroid as above.
30...	20.97	
December 3...	20.13	
6...	19.53	
8...	19.32	Acetonitrile, 69.55 mgms., i. e., 3.6 mgms. per gm. mouse. Died, three-fourths hour.

C. SHEEP THYROID; 0.192 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1907.		
November 28...	18.07	Feeding of cakes, each containing 0.002 gm. thyroid, commenced.
30...	17.85	
December 3...	17.50	
6...	16.77	
7...	17.24	Acetonitrile, 37.93 mgms., i. e., 2.2 mgms. per gm. mouse. Survived.
November 28...	16.00	Thyroid as above.
30...	16.85	
December 3...	16.07	
6...	15.47	
7...	14.92	Acetonitrile, 41.78 mgms., i. e., 2.8 mgms. per gm. mouse. Survived.
November 28...	21.85	Thyroid as above.
30...	20.05	
December 3...	22.40	
6...	20.92	
8...	21.16	Acetonitrile, 69.83 mgms., i. e., 3.3 mgms. per gm. mouse. Survived.
November 28...	17.67	Thyroid as above.
30...	15.59	
December 3...	16.07	
6...	16.17	
8...	15.71	Acetonitrile, 58.13 mgms., i. e., 3.7 mgms. per gm. mouse. Died, one-half hour.

D. CONTROLS.

1907.		
November 28...	21.77	Feeding of cakes without thyroid begun.
30...	21.92	
December 3...	21.09	
6...	20.78	
8...	20.57	Acetonitrile, 5.14 mgms., i. e., 0.25 mgm. per gm. mouse. Died, about 2 hours.
November 28...	24.50	Cakes as above.
30...	23.96	
December 3...	24.51	
6...	24.32	
8...	24.51	Acetonitrile, 7.35 mgms., i. e., 0.3 mgm. per gm. mouse. Died 1½ hours.
November 28...	21.86	Cakes as above.
30...	21.50	
December 3...	21.52	
6...	20.74	
8...	21.50	Acetonitrile, 7.53 mgms., i. e., 0.35 mgm. per gm. mouse. Died 3 hours.

Summary.—The results of the above experiments may be summarized as follows:

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.002	0.061	0.00122	1.1	1.2
B	.006	.061	.00366	3.1	3.6
C	.002	.192	.00384	3.3	3.7
D. Controls					.25

Two thousandths of a gram of thyroid containing 0.192 per cent iodine protected mice against as much acetonitrile as did 0.006 gm. thyroid containing but 0.061 per cent iodine.

Further, with equal amounts of the two thyroid preparations, that containing 0.192 per cent iodine protected against three times as much acetonitrile as did that containing but 0.061 per cent iodine.

Series IV.

A. SHEEP THYROID; 0.1 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
January 15	25.65	Feeding of cakes, each containing 0.001 gm. thyroid, commenced.
18	26.80	
21	26.52	
24	26.50	
26	26.50	Acetonitrile, 37.1 mgms., i. e., 1.4 mgms. per gm. mouse. Survived.
January 15	21.47	Thyroid as above.
18	22.05	
21	21.36	
24	20.00	Acetonitrile, 30 mgms., i. e., 1.5 mgms. per gm. mouse. Survived.
January 15	27.50	Thyroid as above.
18	27.88	
21	27.92	
24	27.88	
25	25.50	Acetonitrile, 43.35 mgms., i. e., 1.7 mgms. per gm. mouse. Died, 1½ hours.
January 15	22.38	Thyroid as above.
18	23.56	
21	22.35	
24	22.22	
25	22.02	Acetonitrile, 44.04 mgms., i e., 2 mgms. per gm. mouse. Died, 2 hours.

B. SHEEP THYROID; 0.19 PER CENT IODINE.

1908.		
January 15	27.74	Feeding of cakes each containing 0.001 gm. thyroid commenced.
18	27.32	
21	27.43	
24	26.70	Acetonitrile, 53.4 mgms., i. e., 2 mgms. per gm. mouse. Survived.
January 15	20.88	Thyroid as above.
18	22.50	
21	22.45	
24	21.58	
25	21.90	Acetonitrile, 54.75 mgms., i. e., 2.5 mgms. per gm. mouse. Survived.
January 15	19.30	Thyroid as above.
18	19.42	
21	18.58	
24	18.58	
26	19.25	Acetonitrile, 51.98 mgms., i. e., 2.7 mgms. per gm. mouse. Survived.
January 15	21.52	Thyroid as above.
18	20.91	
21	21.22	
24	20.69	
26	20.93	Acetonitrile, 62.79 mgms., i. e., 3 mgms. per gm. mouse. Died 1 hour.

C. SHEEP THYROID; 0.1 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
January 15	20.00	Feeding of cakes each containing 0.005 gm. thyroid commenced.
18	20.30	
21	20.27	
24	19.70	Acetonitrile, 68.95 mgms., i. e., 3.5 mgms. per gm. mouse. Survived.
January 15	22.52	Thyroid as above.
18	21.51	
21	21.36	
24	20.72	
25	21.21	Acetonitrile, 95.45 mgms., i. e., 4.5 mgms. per gm. mouse. Survived.
January 15	22.72	Thyroid as above.
18	22.98	
21	22.50	
24	22.22	
26	21.75	Acetonitrile, 108.75 mgms., i. e., 5 mgms. per gm. mouse. Died 1¼ hours.
January 15	21.55	Thyroid as above
18	22.58	
21	22.68	
24	22.70	
26	22.50	Acetonitrile, 123.75 mgms., i. e., 5.5 mgms. per gm. mouse. Died 2½ hours.

D. SHEEP THYROID; 0.19 PER CENT IODINE.

1908.		
January 15	23.13	Feeding of cakes each containing 0.005 gm. thyroid commenced.
18	21.30	
21	22.12	
24	21.06	Acetonitrile, 84.24 mgms., i. e., 4 mgms. per gm. mouse. Survived.
January 15	24.17	Thyroid as above.
18	25.28	
21	24.44	
24	23.40	
26	24.25	Acetonitrile, 133.38 mgms., i. e., 5.5 mgms. per gm. mouse. Died 2 hours.
January 15	21.67	Thyroid as above.
18	21.80	
21	20.90	
24	19.62	
26	19.38	Acetonitrile, 116.3 mgms., i. e., 6 mgms. per gm. mouse. Died 5 hours.

The experiments on the controls for this series were somewhat irregular, but the fatal dose was apparently between 0.4 and 0.5 mg. acetonitrile per gram mouse.

SUMMARY.

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.001	0.1	0.001	1.4	1.7
B	.001	.19	.0019	2 7	3.0
C	.005	.1	.005	4.5	5.0
D	.005	.19	.0095	4.0	5.5
Controls				.4(?)	.5(?)

From A and B it is seen that the thyroid containing 0.19 per cent iodine was nearly twice as active as that containing 0.1 per cent. In C and D the effects (with 0.005 gm. thyroid in each cake) were apparently maximum in each case, so that no difference in the activity of the two preparations was apparent.

SERIES V.

A series very similar to the above is the following:

A. SHEEP THYROID; 0.1 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
February 11....	22.99	Feeding of cakes each containing 0.001 gm. thyroid commenced.
14....	21.66	
17....	22.07	
20....	21.61	
21....	21.74	Acetonitrile, 34.78 mgms., i. e., 1.6 mgms. per gm. mouse. Survived.
February 11....	23.06	Thyroid as above.
14....	21.13	
17....	21.76	
20....	20.94	
21....	21.77	Acetonitrile, 45.72 mgms., i. e., 2.1 mgms. per gm. mouse. Died 2¼ hours.
February 11....	18.50	Thyroid as above.
14....	17.79	
17....	17.47	
20....	17.43	Acetonitrile, 43.58 mgms., i. e., 2.5 mgms. per gm. mouse. Died 3½ hours.
February 11....	20.14	Thyroid as above.
14....	17.48	
17....	17.81	
20....	17.45	Acetonitrile, 52.35 mgms., i. e., 3 mgms. per gm. mouse. Died 2½ hours.

B. SHEEP THYROIDS; 0.19 PER CENT IODINE.

1908.		
February 11....	16.80	Feeding of cakes each containing 0.001 gm. thyroid commenced.
14....	16.02	
17....	16.41	
20....	17.10	Acetonitrile, 34.2 mgms., i. e., 2 mgms. per gm. mouse. Survived.
February 11....	21.25	Thyroid as above.
14....	20.90	
17....	22.48	
20....	17.13	Acetonitrile, 42.83 mgms., i. e , 2.5 mgms. per gm. mouse. Survived.
February 11....	16.38	Thyroid as above
14....	15.29	
17....	15.09	
20....	15.17	
21....	15.59	Acetonitrile, 46.77 mgms., i. e., 3 mgms. per gm. mouse. Survived.
February 11....	21.69	Thyroid as above.
14....	20.46	
17....	21.02	
20....	20.64	
21....	20.90	Acetonitrile, 73.15 mgms., i. e., 3.5 mgms. per gm. mouse. Died 1¼ hours.

C. CONTROLS.

Date.	Weight of mouse.	Remarks.
1908.		
February 11	13.98	Feeding of cakes without thyroid commenced.
14	13.91	
17	14.26	
20	13.75	
21	14.33	Acetonitrile, 4.59 mgms., i. e., 0.32 mgm. per gm. mouse. Survived.
February 11	19.48	Cakes as above.
14	17.70	
17	17.45	
20	16.90	
21	17.42	Acetonitrile, 6.62 mgms., i. e., 0.38 mgm. per gm. mouse. Survived.
February 11	14.98	Cakes as above.
14	13.08	
17	12.72	
20	12.85	
21	13.04	Acetonitrile, 7.17 mgms., i. e., 0.55 mgm. per gm. mouse. Died 4½ hours.

Summary.—The results of the above experiments may be summarized as follows:

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of acetonitrile in mgm. per gm.	
				Recovered.	Died.
A	0.001	0.1	0.0010	1.6	2.1
B	.001	.19	.0019	3.0	3.5
C. Controls				.38	.55

SERIES VI.

In this series the effects of a number of commercial thyroid powders with different percentages of iodine were compared; the effects of different amounts were also compared.

A. SHEEP THYROID; 0.11 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
April 8	13.41	Feeding of cakes each containing 0.001 gm. thyroid commenced.
11	12.68	
14	13.32	
16	13.25	Acetonitrile, 26.50 mgms., i. e., 2 mgms. per gm. mouse. Survived
April 8	12.82	Thyroid as above.
11	12.30	
14	13.26	
16	13.22	
17	13.13	Acetonitrile, 32.83 mgms., i. e., 2.5 mgms. per gm. mouse. Survived.
April 8	14.63	Thyroid as above.
11	14.72	
14	14.06	
16	13.54	
17	13.22	Acetonitrile, 39.66 mgms., i. e., 3 mgms. per gm. mouse. Died 10 hours.
April 8	13.17	Thyroid as above.
11	13.50	
14	12.90	
17	13.02	Acetonitrile, 45.57 mgms., i. e., 3.5 mgms. per gm. mouse. Died 1½ hours.

A[1]. SAME PREPARATION AS ABOVE.

Date.	Weight of mouse.	Remarks.
1908.		
April 8.....	14.30	Feeding of cakes each containing 0.002 gm. thyroid commenced.
11.....	14.96	
14.....	14.67	
16.....	14.20	Acetonitrile, 53.96 mgms., i. e., 3.8 mgms. per gm. mouse. Survived.
April 8.....	12.31	Thyroid as above.
11.....	12.44	
14.....	12.43	
16.....	12.42	
17.....	12.39	Acetonitrile, 50.8 mgms., i. e., 4.1 mgms. per gm. mouse. Survived.
April 8.....	13.21	Thyroid as above.
11.....	13.12	
14.....	13.50	
17.....	13.40	Acetonitrile, 61.64 mgms., i. e., 4.6 mgms. per gm. mouse. Died three-fourths hour.

B. SHEEP THYROID; 0.13 PER CENT IODINE.

1908.		
April 8.....	18.14	Feeding of cakes each containing 0.001 gm. thyroid commenced.
11.....	19.19	
14.....	17.07	
16.....	17.00	Acetonitrile, 37.4 mgms., i. e., 2.2 mgms. per gm. mouse. Survived.
April 8.....	17.64	Thyroid as above.
11.....	19.36	
14.....	20.48	
16.....	20.43	
17.....	20.50	Acetonitrile, 49.2 mgms., i. e., 2.4 mgms. per gm. mouse. Survived.
April 8.....	16.08	Thyroid as above.
11.....	17.31	
14.....	17.15	
16.....	17.86	Acetonitrile, 48.22 mgms., i. e., 2.7 mgms. per gm. mouse. Died 4 hours.
April 8.....	12.34	Thyroid as above.
11.....	13.17	
14.....	12.86	
17.....	12.82	Acetonitrile, 35.9 mgms., i. e., 2.8 mgms. per gm. mouse. Survived.

C. SHEEP THYROID; 0.13 PER CENT IODINE.

1908.		
April 8.....	15.76	Feeding of cakes each containing 0.001 gm. thyroid commenced.
11.....	15.00	
14.....	14.97	
16.....	15.40	Acetonitrile, 33.88 mgms., i. e., 2.2 mgms. per gm. mouse. Survived.
April 8.....	17.80	Thyroid as above.
11.....	18.24	
14.....	18.09	
16.....	18.16	
17.....	18.23	Acetonitrile, 47.4 mgms., i. e., 2.6 mgms. per gm. mouse. Survived.
April 8.....	19.50	Thyroid as above.
11.....	19.26	
14.....	19.02	
17.....	17.28	
18.....	17.07	Acetonitrile, 49.5 mgms., i. e., 2.9 mgms. per gm. mouse. Survived.
April 8.....	13.20	Thyroid as above.
11.....	13.18	
14.....	12.98	
17.....	16.86	Acetonitrile, 52.27 mgms., i. e., 3.1 mgms. per gm. mouse. Died 1½ hours.

D. SHEEP THYROID; 0.1 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
April 8	16.34	Feeding of cakes each containing 0.001 gm. thyroid commenced.
11	16.31	
14	16.06	
16	15.77	Acetonitrile, 36.27 mgms., i. e., 2.3 mgms. per gm. mouse. Survived.
April 8	13.50	Thyroid as above.
11	14.42	
14	14.83	
16	14.43	
17	14.95	Acetonitrile, 40.38 mgms., i. e., 2.8 mgms. per gm. mouse. Survived.
April 8	15.07	Thyroid as above.
11	15.76	
14	14.47	
17	14.22	Acetonitrile, 48.35 mgms., i. e., 3.4 mgms. per gm. mouse. Survived.
April 8	14.12	Thyroid as above.
11	13.92	
14	13.63	
17	12.93	
18	13.42	Acetonitrile, 50.99 mgms., i. e., 3.8 mgms. per gm. mouse. Survived.

D[1]. SAME PREPARATION AS ABOVE.

1908.		
April 8	14.88	Feeding cakes each containing 0.002 gm. thyroid commenced.
11	15.12	
14	14.50	
16	14.50	Acetonitrile, 52.2 mgms., i. e., 3.6 mgms. per gm. mouse. Survived.
April 8	10.94	Thyroid as above.
11	11.30	
14	11.48	
17	10.83	Acetonitrile, 41.15 mgms., i. e., 3.8 mgms. per gm. mouse. Died about 30 hours.
April 8	14.94	Thyroid as above.
11	14.82	
14	13.39	
17	12.88	
18	12.13	Acetonitrile, 47.3 mgms., i. e., 3.9 mgms. per gm. mouse. Died 5 hours.
April 8	13.05	Thyroid as above.
11	13.98	
14	14.06	
17	13.75	
18	13.66	Acetonitrile, 56 mgms., i. e., 4.1 mgms. per gm. mouse. Died 1¾ hours.

E. SHEEP THYROID; 0.19 PER CENT IODINE.

1908.		
April 8	12.40	Feeding cakes each containing 0.001 gm. thyroid commenced.
11	12.70	
14	12.37	
16	12.26	Acetonitrile, 50.27 mgms., i. e., 4.1 mgms. per gm. mouse. Survived.
April 8	13.59	Thyroid as above.
11	13.76	
14	13.45	
16	13.00	
17	12.85	Acetonitrile, 56.54 mgms., i. e., 4.4 mgms. per gm. mouse. Survived.
April 8	17.55	Thyroid as above.
11	18.12	
14	18.02	
16	19.24	Acetonitrile, 88.5 mgms., i. e., 4.6 mgms. per gm. mouse. Died 1½ hours.
April 8	14.74	Thyroid as above.
11	14.48	
14	14.55	
17	14.56	Acetonitrile, 68.43 mgms., i. e., 4.7 mgms. per gm. mouse. Survived.

F. SHEEP THYROID; 0.19 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
April 8	12.02	Feeding of cakes each containing 0.001 gm. thyroid commenced.
11	12.00	
14	11.80	
16	11.11	Acetonitrile, 42.22 mgms., i. e., 3.8 mgms. per gm. mouse. Survived.
April 8	14.37	Thyroid as above.
11	14.08	
14	13.74	
16	12.90	Acetonitrile, 56.76 mgms., i. e., 4.4 mgms. per gm. mouse. Survived.
April 8	13.08	Thyroid as above.
11	13.14	
14	13.36	
16	13.52	
17	12.94	Acetonitrile, 62.11 mgms., i. e., 4.8 mgms. per gm. mouse. Died 2½ hours

SUMMARY.

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.001	0.11	0.0011	2.5	3.0
A[1]	.002	.11	.0022	4.1	4.6
B	.001	.13	.0013	2.8	2.7
C	.001	.13	.0013	2.9	3.1
D	.001	.10	.0010	3.8	.....
D[1]	.002	.10	.0020	3.8	3.9
E	.001	.19	.0019	4.7	4.6
F	.001	.19	.0019	4.4	4.8

In the above series the physiological activity of thyroid containing 0.11, 0.13 (two samples), 0.10, and 0.19 per cent (two samples) of iodine was compared; the preparations were from different manufacturers and were received at different times. Three of the samples with the lower percentages of iodine produced approximately equal effects. The two samples with the higher percentages also produced equal effects; the latter were nearly twice as great as those produced by the former. Moreover, one of the weaker preparations, in twice the amount, produced an effect about equal to that of one of the stronger ones. We encountered in this series one of the few exceptions to the general rule that the physiological activity of a thyroid preparation is parallel to the iodine content. The preparation D, containing 0.1 per cent iodine, was as active as E and F, which contained 0.19 per cent iodine. Possibly there was some error in the weighing of the thyroid or the making of the cakes. In an earlier series with the same preparations the ones with the larger percentages of iodine were about twice as active as the one with the smaller percentage of iodine.

Series VII.

In this series the comparative physiological activity of two samples of a commercial preparation, Thyraden, was determined; the results with a sample of desiccated sheep thyroid containing very nearly the same percentage of iodine are introduced for the sake of comparison.

A. THYRADEN (A); 0.085 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
July 3	15.87	Feeding of cakes each containing 0.001 gm. thyraden commenced.
9	14.43	
11	13.57	
12		Acetonitrile, 8.14 mgms., i. e., 0.6 mgm. per gm. mouse. Survived.
July 3	16.05	Thyraden as above.
9	14.10	
11	14.00	
12		Acetonitrile, 9.24 mgms., i. e., 0.66 mgm. per gm. mouse. Survived.
July 3	14.89	Thyraden as above.
9	13.50	
11	13.33	
12		Acetonitrile, 10 mgms., i. e., 0.75 mgm. per gm. mouse. Died 1½ hours.
July 3	13.42	Thyraden as above.
9	10.41	
11	9.85	Acetonitrile, 9.85 mgms., i. e., 1 mgm. per gm. mouse. Died 1¾ hours.

B. THYRADEN (B); 0.085 PER CENT IODINE.

1908.		
July 3	15.38	Feeding of cakes each containing 0.001 gm. thyraden commenced.
9	14.28	
11	14.44	
12		Acetonitrile, 6.50 mgms., i. e., 0.45 mgm. per gm. mouse. Survived.
July 3	11.37	Thyraden as above.
9	10.97	
11	10.60	
12		Acetonitrile, 5.30 mgms., i. e., 0.5 mgm. per gm. mouse. Survived.
July 3	15.00	Thyraden as above.
9	13.98	
11	12.21	
12		Acetonitrile, 6.72 mgms., i. e., 0.55 mgm. per gm. mouse. Died 2½ hours.
July 3	15.83	Thyraden as above.
9	15.20	
11	15.65	Acetonitrile, 10.96 mgms., i. e., 0.7 mgm. per gm. mouse. Died 2½ hours.

C. SHEEP THYROID; 0.092 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
July 3	15.90	Feeding of cakes each containing 0.001 gm. thyroid begun.
9	14.84	
11	15.05	
12	.....	Acetonitrile, 6.77 mgms., i. e., 0.45 mgm. per gm. mouse. Survived.
July 3	14.14	Thyroid as above.
9	13.44	
11	13.50	
12	.....	Acetonitrile, 8.1 mgms., i. e., 0.6 mgm. per gm. mouse. Died 1¼ hours.
July 3	17.79	Thyroid as above.
9	15.75	
11	15.80	
12	.....	Acetonitrile, 11.85 mgms., i. e., 0.75 mgm. per gm. mouse. Died 2¼ hours.
July 3	12.67	Thyroid as above.
9	11.82	
11	10.90	Acetonitrile, 11.99 mgms., i. e., 1.1 mgms. per gm. mouse. Died 1½ hours.

D. SHEEP THYROID; 0.092 PER CENT IODINE.

1908.		
July 3	13.73	Feeding of cakes each containing 0.0005 gm. thyroid commenced.
9	12.52	
11	12.49	
13	11.95	Acetonitrile, 3.94 mgms., i. e., 0.33 mgm. per gm. mouse. Survived.
July 3	16.90	Thyroid as above.
9	15.74	
11	15.44	
12	.....	Acetonitrile, 5.87 mgms., i. e., 0.38 mgm. per gm. mouse. Died 2¼ hours.
July 3	14.95	Thyroid as above.
9	13.23	
11	12.92	
12	.....	Acetonitrile, 5.81 mgms., i. e., 0.45 mgm. per gm. mouse. Died 2 hours.

E. THYRADEN (A); 0.085 PER CENT IODINE.

1908.		
July 3	19.41	Feeding of cakes each containing 0.002 gm. thyraden commenced.
9	17.13	
11	16.02	Acetonitrile, 19.22 mgms., i. e., 1.2 mgms. per gm. mouse. Survived.
July 3	10.77	Thyraden as above.
9	8.52	
11	8.25	
12	.....	Acetonitrile, 10.72 mgms., i. e., 1.3 mgms. per gm. mouse. Died 2 hours.
July 3	14.15	Thyraden as above.
9	10.66	
11	9.40	
12	.....	Acetonitrile, 15.24 mgms., i. e., 1.62 mgms. per gm. mouse. Died 2½ hours.

F. THYRADEN (B); 0.085 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
July 3	12.98	Feeding of cakes each containing 0.002 gm. thyraden commenced.
9	12.42	
11	11.78	
12		Acetonitrile, 12.96 mgms., i. e., 1.1 mgms. per gm. mouse. Survived.
July 3	14.07	Thyraden as above.
9	12.72	
11	12.77	
12		Acetonitrile, 16.6 mgms., i. e., 1.3 mgms. per gm. mouse. Survived.
July 3	14.56	Thyraden as above.
9	13.80	
11	13.27	
12		Acetonitrile, 18.57 mgms., i. e., 1.4 mgms. per gm. mouse. Died 2¾ hours.
July 3	16.24	Thyraden as above.
9	13.80	
11	13.60	Acetonitrile, 20.40 mgms., i. e., 1.5 mgms. per gm. mouse. Died 3¾ hours.

G. CONTROLS.

1908.		
July 3	18.24	Feeding of cakes without thyroid commenced.
9	14.45	
10		Acetonitrile, 3.03 mgms., i. e., 0.21 mgm. per gm. mouse. Survived.
July 3	15.08	Cakes as above.
9	13.50	
11	13.50	
13	12.95	Acetonitrile, 3.5 mgms., i. e., 0.27 mgm. per gm. mouse. Survived.
July 3	15.89	Cakes as above.
9	13.40	
11	13.50	Acetonitrile, 4.05 mgms., i. e., 0.3 mgm. per gm. mouse. Survived.
July 3	18.08	Cakes as above.
9	17.07	
11	17.63	
12		Acetonitrile, 5.47 mgms., i. e., 0.31 mgm. per gm. mouse. Died 4½ hours.
July 3	16.04	Cakes as above.
9	14.12	
11	14.86	
12		Acetonitrile, 5.05 mgms., i. e., 0.34 mgm. per gm. mouse. Died 3¼ hours.

SUMMARY.

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.001	0.085	0.00085	0.66	0.75
B	.001	.085	.00085	.50	.55
C	.001	.092	.00092	.45	.6
D	.0005	.092	.00046	.33	.38
E	.002	.085	.00170	1.2	1.3
F	.002	.085	.00170	1.3	1.4
G. Controls				.3	.31

These experiments show that the physiological activity of the two samples of Thyraden was approximately the same, in harmony with their equal iodine content. Their activity was not far removed from that of a thyroid preparation containing approximately the same percentage of iodine. Double the amount of Thyraden protected against almost twice the dose of acetonitrile.

Series VIII.

The physiological activity of two samples of commercial thyroid tablets were compared in this series. The tablets were pulverized and amounts containing definite quantities of thyroid were fed.

A. THYROID; 0.38 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
September 24...	18.45	Feeding of cakes each containing 0.001 gm. thyroid commenced.
28...	17.42	
October 2	16.95	Acetonitrile, 23.73 mgms., i. e., 1.4 mgms. per gm. mouse. Survived.
September 24...	22.00	Thyroid as above.
28...	22.36	
October 2	20.82	
3	.....	Acetonitrile, 35.39 mgms., i. e., 1.7 mgms. per gm. mouse. Survived.
September 24...	17.28	Thyroid as above.
28...	17.02	
October 2	15.10	
3	.....	Acetonitrile, 27.18 mgms., i. e., 1.8 mgms. per gm. mouse. Survived.
September 24...	14.70	Thyroid as above.
28...	14.66	
October 2	13.20	Acetonitrile, 26.40 mgms., i. e., 2 mgms. per gm. mouse. Died 3 hours.

B. THYROID; 0.38 PER CENT IODINE.

1908.		
September 24...	13.00	Feeding of cakes each containing 0.005 gm. thyroid commenced.
28...	13.54	
October 2	11.75	Acetonitrile, 21.15 mgms., i. e., 1.8 mgms. per gm. mouse. Survived.
September 24...	15.18	Thyroid as above.
28...	15.20	
October 2	11.86	Acetonitrile, 32.20 mgms., i. e., 2.8 mgms. per gm. mouse. Survived.
September 24...	16.40	Thyroid as above.
28...	15.72	
October 2	13.58	
3	.....	Acetonitrile, 47.46 mgms., i. e., 3.5 mgms. per gm. mouse. Survived.
September 24...	15.85	Thyroid as above.
28...	16.12	
October 2	14.49	
3	.....	Acetonitrile, 60.86 mgms., i. e., 4.2 mgms. per gm. mouse. Survived.

C. THYROID; 0.065 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
September 24	13.35	Feeding of cakes each containing 0.001 gm. thyroid commenced
28	13.34	
October 2	12.54	Acetonitrile, 5.64 mgms., i. e., 0.45 mgm. per gm. mouse. Survived.
September 24	12.70	Thyroid as above.
28	12.36	
October 2	11.58	
3		Acetonitrile, 5.79 mgms., i. e., 0.50 mgm. per gm. mouse. Survived.
September 24	16.10	Thyroid as above.
28	16.24	
October 2	15.97	
3		Acetonitrile, 9.26 mgms., i. e., 0.58 mgm. per gm. mouse. Died 2¾ hours.
September 24	20.88	Thyroid as above.
28	20.62	
October 2	17.73	Acetonitrile, 12.41 mgms., i. e., 0.7 mgm. per gm. mouse. Died 1 hour.

D. THYROID; 0.065 PER CENT IODINE.

1908.		
September 24	19.55	Feeding of cakes each containing 0.005 gm. thyroid commenced.
28	19.90	
October 2	19.13	Acetonitrile, 22.96 mgms., i. e., 1.2 mgms. per gm. mouse. Survived.
September 24	13.89	Thyroid as above.
28	13.70	
October 2	13.60	
3		Acetonitrile, 21.76 mgms., i. e., 1.6 mgms. per gm. mouse. Survived.
September 24	18.60	Thyroid as above.
28	18.20	
October 2	17.00	
3		Acetonitrile, 32.3 mgms., i. e., 1.9 mgms. per gm. mouse. Survived.
September 24	13.15	Thyroid as above.
28	13.06	
October 2	10.55	Acetonitrile, 21.10 mgms., i. e., 2 mgms. per gm. mouse. Died 2½ hours.

SUMMARY.

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.001	0.38	0.0038	1.8	2.0
B	.005	.38	.019	4.2	
C	.001	.065	.00065	.5	.58
D	.005	.065	.00325	1.9	2.00
E. Controls					.1

Five times as much thyroid was required in D as in A to produce a given physiological effect; this difference corresponds fairly closely with the differences in the percentages of iodine.

Many other experiments with results similar to the above were performed; a number of them will be reported later in other connections. More than twenty preparations of commercial desiccated thyroids were examined and, with possibly one exception, their

activity was parallel to the iodine content. In the exceptional case the activity seemed to be somewhat less than was anticipated from the percentage of iodine; possibly the thyroid had been overheated in the process of drying or had undergone some decomposition, although there is little evidence that such treatment will materially reduce the activity of thyroid.

Occasionally we encountered a series of experiments in which irregular results were obtained. In such cases the experiments were repeated at least twice and concordant results were obtained. The irregularities had probably resulted from some error in making the cakes or the amount of thyroid fed had been too large or too small to give results which could be compared, or perhaps the mice had not been kept under uniform conditions before the thyroid was fed.

As pointed out elsewhere,[a] we have been able to foretell with considerable accuracy the iodine content of a thyroid preparation by comparing its physiological activity with that of another preparation the iodine content of which was known.

iii. EXPERIMENTS WITH THYROID FROM VARIOUS ANIMALS.

One of the present writers[b] has shown in a previous publication that there is a parallelism between the amount of iodine and the physiological activity of the thyroid of a number of animals (guinea pig, cat, beef, sheep, hog, etc.). Thus a sample of hog thyroid with 0.33 per cent iodine was about six times as active as one of guinea pig thyroid with 0.05 per cent; a sample of sheep thyroid with 0.176 per cent was approximately three times as active as the guinea pig and but one-half as active as the hog thyroid, etc.

We have been able to extend these observations to the thyroids of a large number of wild animals.[c] The results were similar, but the parallelism was not as strict as when thyroids of the same species were compared. The following illustrations may be given: The thyroid of a deer with 0.193 per cent iodine was about three times as active as that of a Barbary sheep with 0.075 per cent; that of the Barbary sheep was more than twice as active as that of a sea lion with 0.022 per cent iodine. The thyroid of a cat with 0.08 per cent iodine was about as active as that of the Barbary sheep with 0.075 per cent, but it was distinctly more active than that of a dog with 0.111 per cent.

If we accept the view that iodine free thyreoglobulin has a low degree of physiological activity, then such slight discrepancies may be explained on the supposition that different thyroids, with equal

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[a] R. Hunt and A. Seidell, J. Am. M. Ass., Chicago, 1908, **51,** p. 1385.

[b] R. Hunt, J. Am. M. Ass., Chicago, 1907, **49,** p. 1324.

[c] A few of these results were quoted on pp. 45 and 48.

percentages of iodine, have unequal amounts of this iodine-free material; the latter has a slight but distinct action.

Results similar to the above were obtained with the thyroid both of normal dogs and of dogs which had been fed potassium iodide or iodoform. We also found a parallelism between the iodine content and the physiological activity of a large number of normal and pathological human thyroids. These results will be published in detail in another connection, but the following summaries of a few experiments with human thyroids may be quoted to show how close is the parallelism between iodine content and physiological activity:

SERIES I.—HUMAN THYROID.

No. of specimen.	Gm. thyroid fed daily.	Percentage of iodine.	Mgm. I in thyroid fed.	Fatal dose of acetonitrile in mgm. per gm.	
				Recovered.	Died.
23927	0.001	0.05	0.0005	.....	0.18
23821	.001	.23	.0023	0.7	.9
23807	.001	.26	.0026	.95	1.0
Controls	.....	.....	.....	.13	.14

SERIES II.—HUMAN THYROID.

23927	0.001	0.05	0.0005	0.08	0.096
23807	.001	.26	.0026	.6	.66
23785	.001	.45	.0045	.9	1.00

SERIES III.—HUMAN THYROID.

23927	0.001	0.05	0.0005	0.27	0.28
23821	.001	.23	.0023	2.0	.....
23785	.001	.45	.0045	3.6	.....
Controls	.....	.....	.....	.21	.21

b. Experiments on Rats.

The feeding of thyroid to rats lowers their resistance to acetonitrile; the result is thus just the opposite to that which occurs in the case of mice. This was, however, the result we had expected in all classes of animals. For it seemed probable, if acetonitrile is poisonous only as a result of the liberation of hydrocyanic acid from it in the body, that whatever stimulates metabolism would also hasten the decomposition of the nitrile, with a corresponding greater production of hydrocyanic acid. We do not know whether this is the correct explanation of the effect of thyroid feeding in the case of the rat or not. Some light upon this question could probably be obtained by a study of the excretion in the urine of sulphocyanates. In one experiment of this character no difference was found between the amounts of sulphocyanic acid in the urine of normal and thyroid fed rats after the administration of acetonitrile.[a]

[a] It may be mentioned in this connection that negative results were obtained in similar experiments upon dogs.

In the present work we were chiefly interested in determining if there is a relation between the percentage of iodine in different thyroid preparations and their effect upon the resistance of rats to acetonitrile. The following experiments show that there is such a relation and that the degree of activity is in general parallel with the iodine content:

SERIES I.

A. THYRADEN; 0.085 PER CENT IODINE.

Date.	Weight of rat.	Remarks.
1908.		
June 27	32	Feeding of cakes each containing 0.001 gm. thyraden commenced.
July 1	31	
6	30	Acetonitrile, 30 mgms., i. e., 1 mgm. per gm. rat. Survived.
June 27	65	Thyraden as above.
July 1	68	
6	62	Acetonitrile, 86.8 mgms., i. e., 1.4 mgms. per gm. rat. Survived.
June 27	48	Thyraden as above.
July 1	44	
6	45	
7		Acetonitrile, 76.5 mgms., i. e., 1.7 mgms. per gm. rat. Died 5 hours.
June 27	33	Thyraden as above.
July 1	34	
6	32	
7		Acetonitrile, 57.6 mgms., i. e., 1.8 mgms. per gm. rat. Survived.

B. SHEEP THYROID; 0.11 PER CENT IODINE.

1908.		
June 27	29	Feeding of cakes each containing 0.001 gm. thyroid commenced.
July 1	29	
6	28	
7		Acetonitrile, 25.2 mgms., i. e., 0.9 mgm. per gm. rat. Survived.
June 27	54	Thyroid as above.
July 1	53	
6	54	Acetonitrile, 54 mgms., i. e., 1 mgm. per gm. rat. Survived.
June 27	31	Thyroid as above.
July 1	30	
6	29	Acetonitrile, 31.9 mgms., i. e., 1.1 mgms. per gm. rat. Died 3½ hours.
June 27	63	Thyroid as above.
July 1	61	
6	54	Acetonitrile, 70.2 mgms., i. e., 1.3 mgms. per gm. rat. Died about 3 hours.

C. SHEEP THYROID; 0.21 PER CENT IODINE.

1908.		
June 27	43	Feeding of cakes each containing 0.001 gm. thyroid commenced.
July 1	42	
6	42	Acetonitrile, 1.68 mgms., i. e., 0.04 mgm. per gm. rat. Survived.
June 27	29	Thyroid as above.
July 1	29	
6	28	
7		Acetonitrile, 15.40 mgms., i. e., 0.55 mgm. per gm. rat. Survived.
June 27	40	Thyroid as above.
July 1	41	
6	39	Acetonitrile, 27.3 mgms., i. e., 0.7 mgm. per gm. rat. Died 1½–2 hours.
June 27	61	Thyroid as above.
July 1	58	
6	54	Acetonitrile, 54 mgms., i. e., 1 mgm. per gm. rat. Died 1¼ hours.

D. SHEEP THYROID; 0.11 PER CENT IODINE.

Date.	Weight of rat.	Remarks.
1908.		
June 27	33	Feeding of cakes each containing 0.0005 gm. thyroid commenced.
July 1	32	
6	30	Acetonitrile, 45 mgms., i. e., 1.5 mgms. per gm. rat. Survived.
June 27	29	Thyroid as above.
July 1	30	
6	30	
7	.....	Acetonitrile, 48 mgms., i. e., 1.6 mgms. per gm. rat. Survived.
June 27	46	Thyroid as above.
July 1	42	
6	45	
7	.....	Acetonitrile, 81 mgms., i. e., 1.8 mgms. per gm. rat. Died 4¾ hours.
June 27	58	Thyroid as above.
July 1	57	
6	55	Acetonitrile, 104.5 mgms., i. e., 1.9 mgms. per gm. rat. Died 1¼ hours.

E. CONTROLS.

1908.		
June 27	34	Feeding of cakes without thyroid commenced.
July 1	33	
6	34	Acetonitrile, 102 mgms., i. e., 3 mgms. per gm. rat. Survived.
June 27	30	Feeding of cakes as above.
July 1	31	
6	30	
7	.....	Acetonitrile, 99 mgms., i. e., 3.3 mgms. per gm. rat. Survived.
June 27	31	Cakes as above.
July 1	29	
6	29	
7	.....	Acetonitrile, 104.4, mgms., i. e., 3.6 mgms. per gm. rat. Survived.
June 27	52	Cakes as above.
July 1	49	
6	49	
7	.....	Acetonitrile, 196 mgms., i. e., 4 mgms. per gm. rat. Died 4 hours.

Summary.—The above results may be tabulated as follows:

	Gm. thyroid in each cake.	Percentage of iodine in thyroid.	Mgm. I in thyroid in each cake.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.001	0.085	0.00085	1.4	1.7
B	.001	.11	.0011	1.0	1.1
C	.001	.21	.0021	.55	.7
D	.0005	.11	.00055	1.6	1.8
E. Controls	.....	.....	.....	3.6	4.0

These results show that the thyroids with the higher percentages of iodine were more active in diminishing the resistance of rats to acetonitrile than was that with the lowest percentage. One-half of a milligram of thyroid containing 0.11 per cent iodine was nearly as active as a milligram of thyroid with 0.085 per cent iodine.

Series II.

Various amounts of the thyroid of several different animals with different percentages of iodine were fed in this series. The total amount of iodine fed did not vary greatly and the physiological effects were not very different.

A. DOG THYROID; 0.104 PER CENT IODINE.

Date.	Weight of rat.	Remarks.
1907.		
July 6	124	Feeding of cakes each containing 0.0035 gm. thyroid commenced.
8	123	
11	120	
15	119	
17	118	Acetonitrile, 94.4 mgms., i. e., 0.8 mgm. per gm. rat. Survived.
July 6	107	Thyroid as above.
8	104	
11	100	
15	98	
17	98	Acetonitrile, 98 mgms., i. e., 1 mgm. per gm. rat. Died 3 hours.
July 6	73	Thyroid as above.
8	70	
11	68	
15	64	
16	63	Acetonitrile, 81.9 mgms., i. e., 1.3 mgms. per gm. rat. Died about 3 hours.
July 6	79	Thyroid as above.
8	77	
11	74	
15	68	
16	70	Acetonitrile, 126 mgms., i. e., 1.8 mgms. per gm. rat. Died 3½ hours.

B. SHEEP THYROID; 0.176 PER CENT IODINE.

1907.		
July 6	122	Feeding of cakes each containing 0.002 gm. thyroid commenced.
8	119	
11	114	
15	105	
16	105	Acetonitrile, 94.5 mgms., i. e., 0.9 mgm. per gm. rat. Survived.
July 6	106	Thyroid as above.
8	106	
11	104	
15	101	
17	102	Acetonitrile, 102 mgms., i. e., 1 mgm. per gm. rat. Survived.
July 6	73	Thyroid as above.
8	69	
11	66	
15	62	
17	64	Acetonitrile, 76.8 mgms., i. e., 1.2 mgms. per gm. rat. Died 2½ hours.
July 6	76	Thyroid as above.
8	71	
11	70	
15	68	
16	68	Acetonitrile, 102 mgms., i. e., 1.5 mgms. per gm. rat. Died 4 hours.

C. HOG THYROID; 0.33 PER CENT IODINE.

Date.	Weight of rat.	Remarks.
1907.		
July 6	142	Feeding of cakes each containing 0.001 gm. thyroid commenced.
8	144	
11	113	
15	106	
17	103	Acetonitrile, 61.8 mgms., i. e., 0.6 mgm. per gm. rat. Survived.
July 6	88	Thyroid as above.
8	84	
11	81	
15	79	
17	80	Acetonitrile, 64 mgms., i. e., 0.8 mgm. per gm. rat. Died 3 hours.
July 6	85	Thyroid as above.
8	82	
11	79	
15	78	
16	77	
17	78	Acetonitrile, 85.8 mgms., i. e., 1.1 mgms. per gm. rat. Died 3 hours.
July 6	88	Thyroid as above.
8	87	
11	85	
15	83	
16	84	Acetonitrile, 109.2 mgms., i. e., 1.3 mgms. per gm. rat. Died about 8 hours

D. CONTROLS.

1907.		
July 6	68	Feeding of cakes without thyroid commenced.
8	70	
11	70	
15	67	
16	67	Acetonitrile, 174 mgms., i. e., 2.6 mgms. per gm. rat. Survived.
July 6	103	Cakes as above
8	100	
11	100	
15	97	
16	96	Acetonitrile, 268.8 mgms., i. e., 2.8 mgms. per gm. rat. Survived.
July 6	109	Cakes as above.
8	112	
11	98	
15	85	
17	85	Acetonitrile, 246.5 mgms., i. e., 2.9 mgms. per gm. rat. Survived.
July 6	88	Cakes as above.
8	87	
11	86	
15	85	Acetonitrile, 255 mgms., i. e., 3 mgms. per gm. rat. Died 5 hours.
July 6	107	Cakes as above.
8	91	
11	92	
15	92	
16	90	
17	90	
18	85	Acetonitrile, 275.9 mgms., i. e., 3. 1 mgms. per gm. rat. Survived.

SUMMARY.

	Gm. thyroid in each cake.	Percentage of iodine in thyroid.	Mgm. I in thyroid of each cake.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.0035	0.104	0.0035	0.8	1.0
B	.002	.176	.0035	1.0	1.2
C	.001	.33	.0033	.6	.8
D. Controls				3.1	3.0

These results show that in order to cause approximately equal physiological effects (as measured by the diminished resistance of the rats to acetonitrile) it was necessary to feed larger amounts of the iodine poor than of the iodine rich thyroid.

SERIES III.

In this series the physiological activity of dog thyroid, the iodine content of which had been increased by the administration of iodoform, was determined. As the results of these experiments are given in detail in Part II (p. 103–5) of this bulletin, only a summary will be given here.

	Gm. thyroid in each cake.	Percentage of iodine.	Mgm. I in thyroid of each cake.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.0005	0.111	0.00055	1.8	2.1
B	.0005	.300	.00150	1.3	1.5
C	.0015	.111	.00166	1.2	1.3
D	.003	.111	.00333	.9	1.0
E	.001	.300	.00300	.5	.6
F. Controls				2.9	3.0

GENERAL CONCLUSIONS.

The above series of experiments show that there is a close parallelism between the iodine content of the thyroid and its physiological activity as measured by its effect in diminishing the resistance of rats to acetonitrile.

2. EXPERIMENTS WITH MORPHINE.

It has been shown above that the feeding of thyroid causes an alteration in the resistance of animals to acetonitrile. The effect differs in different species; there is an increased resistance in the case of mice and diminished resistance in rats. In both cases, however, the activity of the thyroid is parallel with its iodine content.

Experiments will now be described in which the effect of feeding thyroid upon the resistance of animals to another poison, morphine,[a] was determined. Experiments were made upon mice, rats, and guinea pigs. The resistance of all of these animals to morphine was lowered by the feeding of thyroid and there was a general parallelism between the activity of the different thyroid preparations in this respect and their iodine content.

In performing experiments with morphine it is necessary to observe the precautions noted in the experiments with acetonitrile. Different

[a] Similar results were obtained in a few experiments with acetyl-morphine ("heroin") and with codeine.

lots of animals react very differently to morphine; thus in our experiments the fatal dose (by subcutaneous injection) for normal animals has ranged from 0.2 to 0.42 mgm. per gram weight for rats,[a] from 0.16 to 0.45 mgm. for mice,[b] and from 0.6 to 0.75 mgm. for guinea pigs.[c] We were able to find definite relations between the resistance of mice to morphine and the diet which they had received; whether in addition to this effect of diet the age of the animals, their weight or the season, temperature, etc., has an influence we have not been able to definitely determine. Animals which have been kept under uniform conditions react very uniformly to the poison, and it is possible to determine the fatal dose with great accuracy.

These experiments afford another illustration of the folly of determining the "fatal dose" of a poison at the beginning of a long series of experiments, or, as is often done, accepting such a figure as determined by some other investigator and using it as a "control" in a new series of experiments.

a. Experiments on White Rats.

Series I.

A. SHEEP THYROID; 0.176 PER CENT IODINE.

Date.	Weight of rat.	Remarks.
1907.		
May 30	87	Feeding of cakes each containing 0.005 gm. thyroid begun.
June 3	81	
7	77	
9	75	Morphine sulphate, 2.25 mgms., i. e., 0.03 mgm. per gm. rat. Survived.
May 30	88	Thyroid as above.
June 3	84	
7	79	
9	77	Morphine sulphate, 3.85 mgms., i. e., 0.05 mgm. per gm. rat. Survived.
May 30	107	Thyroid as above.
June 3	98	
7	94	
9	92	Morphine sulphate, 6.44 mgms., i. e., 0.07 mgm. per gm. rat. Survived.

[a] T. Sollmann (Textbook of Pharmacology, 2d ed., 1906, p. 954) places the fatal dose of morphine for rats at 0.45 mgm. per gram body weight.

[b] J. Morgenroth (Berl. klin. Wchnschr., 1903, **40**, p. 471) found the fatal dose of morphine hydrochloride for mice in Frankfort on the Main, to be about 0.93 mgm. per gram.

[c] T. Sollmann (l. c.) places the fatal dose of morphine for guinea pigs at 0.7 mgm. per gram.

B. HOG THYROID; 0.33 PER CENT IODINE.

Date.	Weight of rat.	Remarks.
1907.		
May 30	78	Feeding of cakes each containing 0.005 gm. thyroid begun.
June 3	71	
7	72	
9	67	Morphine sulphate, 1.68 mgms., i. e., 0.025 mgm. per gm. rat. Survived.
May 30	77	Thyroid as above.
June 3	72	
7	70	
9	68	Morphine sulphate, 2.72 mgms., i. e., 0.04 mgm. per gm. rat. Died in 3 hours.
May 30	101	Thyroid as above.
June 3	97	
7	89	
9	90	Morphine sulphate, 4.5 mgms., i. e., 0.05 mgm. per gm. rat. Died 1¾ hours.

C. CONTROLS.

1907.		
May 30	93	Feeding of plain cakes begun.
June 3	91	
7	91	
9	91	Morphine sulphate, 27.3 mgms., i. e., 0.3 mgm. per gm. rat. Survived.
May 30	79	Cakes as above.
June 3	75	
7	73	
9	74	Morphine sulphate, 25.9 mgms., i. e., 0.35 mgm. per gm. rat. Survived.
May 30	92	Cakes as above.
June 3	83	
7	82	
9	80	Morphine sulphate, 32.0 mgms., i. e., 0.4 mgm. per gm. rat. Survived.
June 1	46	Cakes as above.
5	45	
7	45	
11	43	Morphine sulphate, 18.06 mgms., i. e., 0.42 mgm. per gm. rat. Died 2 hours.

Summary.—The results of these experiments may be summarized as follows:

	Gm. thyroid in each cake.	Percentage of iodine in thyroid.	Mgm. I in thyroid of each cake.	Average loss of weight in per cent of original weight.	Fatal dose of morphine in mg. per gm.	
					Recovered.	Died.
A	0.005	0.176	0.0088	13.4	0.07	.....
B	.005	.33	.0165	12.1	.025	0.04
C. Controls	.....	.....	.....	7.1	.40	.42

Unfortunately the fatal dose of morphine for rats which had received sheep thyroid, A, was not determined; it was probably twice as great as that for those which had received hog thyroids, B. The sheep thyroid contained about one-half as much iodine as the hog thyroid. Rats receiving the hog thyroid died from one-tenth the amount of morphine necessary to kill the controls. The rats of

all three series lost weight; the controls lost 7.1 per cent. Evidently the exclusive diet of crackers is not suitable for rats. The loss of weight caused by the thyroid was slight if that which would have probably been caused by the crackers alone is deducted, and probably had nothing to do with the increased susceptibility of the animals to morphine.

SERIES II.

A. THYRADEN; 0.085 PER CENT IODINE.

Date.	Weight of rat.	Remarks.	
1908.			
July 14	57	Feeding of cakes each containing 0.001 gm. thyraden begun.	
18	56		
22	55	Morphine sulphate, 4.95 mgms., i. e., 0.09 mgm. per gm. rat.	Survived.
July 14	54	Thyraden as above.	
18	51		
22	49	Morphine sulphate, 5.88 mgms., i. e., 0.12 mgm. per gm. rat.	Survived.
July 14	52	Thyraden as above.	
18	48		
22	48	Morphine sulphate, 7.20 mgms., i. e., 0.15 mgm. per gm. rat.	Died in 5 hours.
July 14	80	Thyraden as above.	
18	78		
22	75		
23	.....	Morphine sulphate, 12.0 mgms., i. e., 0.16 mgm. per gm. rat.	Survived.

B. SHEEP THYROID; 0.12 PER CENT IODINE.

1908.			
July 14	60	Feeding of cakes each containing 0.001 gm. thyroid begun.	
18	55		
22	54	Morphine sulphate, 4.32 mgms., i. e., 0.08 mgm. per gm. rat.	Survived.
July 14	66	Thyroid as above.	
18	65		
22	66	Morphine sulphate, 7.26 mgms., i. e., 0.11 mgm. per gm. rat.	Survived.
July 14	54	Thyroid as above.	
18	51		
22	53		
23	.....	Morphine sulphate, 6.89 mgms., i. e., 0.13 mgm. per gm. rat.	Survived.
July 14	60	Thyroid as above.	
18	58		
22	59		
23	.....	Morphine sulphate, 8.85 mgms., i. e., 0.15 mgm. per gm. rat.	Died in 2 hours.

C. SHEEP THYROID; 0.19 PER CENT IODINE.

1908.			
July 14	45	Feeding of cakes each containing 0.001 gm. thyroid begun.	
18	41		
22	40	Morphine sulphate, 1.60 mgms., i. e., 0.04 mgm. per gm. rat.	Survived.
July 14	42	Thyroid as above.	
18	40		
22	38		
23	.....	Morphine sulphate, 1.90 mgms., i. e., 0.05 mgm. per gm. rat.	Died 4 hours.
July 14	44	Thyroid as above.	
18	43		
22	43	Morphine sulphate, 2.58 mgms., i. e., 0.06 mgm. per gm. rat.	Died 4 hours.

D. SHEEP THYROID; 0.2 PER CENT IODINE.

Date.	Weight of rat.	Remarks.
1908.		
July 14	33	Feeding of cakes each containing 0.001 gm. thyroid begun.
18	31	
22	30	Morphine sulphate, 1.50 mgms., i. e., 0.05 mgm. per gm. rat. Survived.
July 14	60	Thyroid as above.
18	54	
22	53	
23	.....	Morphine sulphate, 3.18 mgms., i. e., 0.06 mgm. per gm. rat. Died 5 hours.
July 14	65	Thyroid as above.
18	61	
22	62	
23	.....	Morphine sulphate, 4.34 mgms., i. e., 0.07 mgm. per gm. rat. Died 2 hours.
July 14	40	Thyroid as above.
18	40	
22	38	Morphine sulphate, 3.04 mgms., i. e., 0.08 mgm. per gm. rat. Died 5½ hours.

E. SHEEP THYROID; 0.19 PER CENT IODINE.

1908.		
July 14	61	Feeding of cakes each containing 0.0005 gm. thyroid begun.
18	59	
22	59	Morphine sulphate, 5.31 mgms., i. e., 0.09 mgm. per gm. rat. Survived.
July 14	87	Thyroid as above.
18	83	
22	81	Morphine sulphate, 8.91 mgms., i. e., 0.11 mgm. per gm. rat. Survived.
July 14	52	Thyroid as above.
18	49	
22	48	Morphine sulphate, 5.76 mgms., i. e., 0.12 mgm. per gm. rat. Died 1¼ hours.
July 14	75	Thyroid as above.
18	71	
22	74	
23	.....	Morphine sulphate, 9.62 mgms., i. e., 0.13 mgm. per gm. rat. Died 1½ hours.

F. SHEEP THYROID; 0.2 PER CENT IODINE.

1908.		
July 14	47	Feeding of cakes each containing 0.0005 gm. thyroid begun.
18	46	
22	46	Morphine sulphate, 3.68 mgms., i. e., 0.08 mgm. per gm. rat. Survived.
July 14	48	Thyroid as above.
18	50	
22	47	
23	.....	Morphine sulphate, 4.23 mgms., i. e., 0.09 mgm. per gm. rat. Survived.
July 14	50	Thyroid as above.
18	48	
22	49	
23	.....	Morphine sulphate, 5.29 mgms., i. e., 0.11 mgm. per gm. rat. Died 3½ hours.
July 14	47	Thyroid as above.
18	45	
22	43	Morphine sulphate, 5.16 mgms., i. e., 0.12 mgm. per gm. rat. Died 12 hours.

All of the controls (i. e., rats which had received no thyroid) died, so that we are unable to state the fatal dose. The smallest dose which killed was 0.2 mgm. per gram.

Summary.—The results of these experiments may be summarized as follows:

	Gm. thyroid in each cake.	Percentage of iodine in thyroid.	Mgm. I in thyroid in each cake.	Loss of weight in percent of original weight.	Fatal dose of morphine in mgm. per gm.	
					Recovered.	Died.
A	0.001	0.085	0.00085	6.6	0.16	0.15
B	.001	.12	.0012	3.3	.13	.15
C	.001	.19	.0019	7.6	.04	.05
D	.001	.2	.0020	7.6	.05	.06
E	.0005	.19	.00095	4.7	.11	.12
F	.0005	.2	.001	3.6	.09	.11
G controls				1.0		.20

The fatal dose of morphine sulphate for the rats which had received the thyroid with the higher percentages of iodine (0.19 to 0.2) was less than one-half as great as that for those which had received the thyroid with the lower percentages of iodine (0.085 and 0.12). The fatal doses were about the same when but one-half as much of the iodine rich thyroid as of the iodine poor thyroid was fed. There were but slight losses of weight.

Series III.

In this series (which was not very complete) the effects of feeding dog thyroid, the iodine content of which had been increased by the administration of iodoform to the dogs, were determined. Since the experiments will be given in detail in Part II (p. 107–9) of this bulletin only the summary is given here.

	Gm. thyroid in each cake.	Percentage of iodine in thyroid.	Mgm. I in thyroid in each cake.	Loss of weight in percent of original weight.	Fatal dose of morphine in mgm. per gm.	
					Recovered.	Died.
A	0.0005	0.111	0.00055	7.0	0.25	
B	.0005	.3	.0015	7.6	.20	0.25
C	.0015	.111	.00166	2.4		.25
D	.003	.111	.00333	.0	.16	.20
E	.001	.106	.00106	5.5	.25	
F	.001	.3	.00300	14.0		.20
G controls				9.1	.39	.40

These experiments show that with equal amounts of thyroid containing different percentages of iodine those with the higher percentages of iodine caused the greater lowering of resistance to morphine; also that in order to obtain equal physiological effects it was necessary to feed much more of the iodine poor than of the iodine rich thyroid. Loss of weight can not explain the increased susceptibility of the rats to morphine, for with but one exception there was no loss of weight greater than that which could be ascribed to the exclusive cracker diet.

SERIES IV.

The following experiments may be quoted for the purpose of illustrating how markedly the resistance of rats to morphine may be reduced by the feeding of thyroid rather than because they bring out the effects of different iodine percentages. The amounts of thyroid fed were selected so as to make the total amount of iodine approximately equal in all cases. Unfortunately the experiments were not sufficiently numerous for us to determine the minimum lethal doses in all cases.

A. DOG THYROIDS; 0.111 PER CENT IODINE.

Date.	Weight of rat.	Remarks.
1907.		
June 25	189	Feeding of cakes each containing 0.003 gm. thyroid begun.
29	181	
July 3	181	
5	182	Morphine sulphate, 7.28 mgms., i. e., 0.04 mgm. per gm. rat. Died 13 hours.
June 25	192	Thyroid as above.
29	186	
July 3	183	
6	176	Morphine sulphate, 9.68 mgms., i. e., 0.055 mgm. per gm. rat. Died 4 hours.
June 25	152	Thyroid as above.
29	142	
July 3	138	
5	138	Morphine sulphate, 9.66 mgms., i. e., 0.07 mgm. per gm. rat. Died 9 hours.

B. THYROID OF GUINEA PIG; 0.05 PER CENT IODINE.

1907.		
June 25	116	Feeding of cakes each containing 0.007 gm. thyroid begun.
29	117	
July 3	118	
5	118	Morphine sulphate, 10.62 mgms., i. e., 0.09 mgm. per gm. rat. Survived.
June 25	156	Thyroid as above.
29	155	
July 3	155	
5	156	Morphine sulphate, 15.63 mgms., i. e., 0.1 mgm. per gm. rat. Died 3½ hours.
June 25	106	Thyroid as above.
29	101	
July 3	100	
5	101	Morphine sulphate, 12.12 mgms., i. e., 0.12 mgm. per gm. rat. Died 4½ hours.

C. HOG THYROID; 0.33 PER CENT IODINE.

1907.		
June 25	141	Feeding of cakes each containing 0.001 gm. thyroid begun.
29	134	
July 3	133	
5	133	Morphine sulphate, 3.99 mgms., i. e., 0.03 mgm. per gm. rat. Died 2¼ hours.
June 25	138	Thyroid as above.
29	134	
July 3	135	
5	132	Morphine sulphate, 5.28 mgms., i. e., 0.04 mgm. per gm. rat. Died 2¾ hours.
June 25	155	Thyroid as above.
29	149	
July 3	146	
5	145	Morphine sulphate, 8.7 mgms., i. e., 0.06 mgm. per gm. rat. Died 2 hours.

D. SHEEP THYROID; 0.176 PER CENT IODINE.

Date.	Weight of rat.	Remarks.
1907.		
June 25	114	Feeding of cakes each containing 0.002 gm. thyroid begun.
29	110	
July 3	111	
5	108	Morphine sulphate, 3.24 mgms., i. e., 0.03 mgm. per gm. rat. Died 20 hours.
June 25	158	Thyroid as above.
29	150	
July 3	150	
6	150	Morphine sulphate, 6.75 mgms., i. e., 0.045 mgm. per gm. rat. Died 2 hours.
June 25	127	Thyroid as above.
29	120	
July 3	121	
5	120	Morphine sulphate, 7.2 mgms., i. e., 0.06 mgm. per gm. rat. Died 5½ hours.

E. CONTROLS.

1907.		
June 25	121	Feeding of plain cakes begun.
29	109	
July 3	109	
4	111	Morphine sulphate, 27.75 mgms., i. e., 0.25 mgm. per gm. rat. Survived.
June 25	100	Cakes as above.
29	97	
July 3	96	
4	96	Morphine sulphate, 28.8 mgms., i. e., 0.30 mgm. per gm. rat. Survived.
June 25	119	Cakes as above.
29	120	
July 3	119	
6	119	Morphine sulphate, 36.89 mgms., i. e., 0.31 mgm. per gm. rat. Died 5½ hours.
June 25	73	Cakes as above.
29	71	
July 3	72	
5	70	Morphine sulphate, 22.4 mgms., i. e., 0.32 mgm. per gm. rat. Died 8 hours.
June 25	81	Cakes as above.
29	78	
July 3	74	
5	79	Morphine sulphate, 27.65 mgms., i. e., 0.35 mgm. per gm. rat. Died 2½ hours.

Summary.—The results of the above experiments are shown in the following table:

	Gm. thyroid in each cake.	Percentage of iodine in thyroid.	Mgm. I in thyroid in each cake.	Loss of weight in per cent of original weight.	Fatal dose of morphine in mgm. per gm.	
					Recovered.	Died.
A	0.003	0.111	0.0033	7.0	.....	0.04
B	.007	.05	.0035	.8	0.09	.10
C	.001	.33	.0033	5.5	.....	.03
D	.002	.176	.00352	5.2	.....	.03
E. Controls	.....	.....	.....	4.0	.30	.31

Although the amounts of thyroid fed varied widely (from 0.001 gm. to 0.007 gm.), there was approximately the same amount of iodine in all cases and, with one exception, the lowering of the resistance seemed to be about equal. In all cases except one fully ten times as much morphine was required to kill the controls as to kill those which had received thyroid. The thyroid caused practically no loss of weight; the very slight loss which occurred can be attributed to the cracker diet.

SUMMARY OF EXPERIMENTS ON RATS.

The above experiments show very clearly that the resistance of rats to morphine is lowered by the feeding of thyroid. In two series the fatal dose for the thyroid-fed rats was but one-tenth that for the controls. They also show that the activity of different thyroid preparations in this respect is closely parallel to their iodine content. It would doubtlessly be possible to determine with a fair degree of accuracy the percentage of iodine in a thyroid preparation by comparing its physiological activity with that of another preparation containing a known percentage of iodine. The increased susceptibility to morphine is entirely independent of any loss of weight; it can evidently not be attributed to a "general lowering of resistance" such as may be supposed to occur when there is a loss of weight from starvation.[a]

b.—Experiments on Mice.

The results of the experiments on mice were somewhat irregular. There was invariably, however, an increased susceptibility to morphine as a result of the feeding of thyroid. As a rule the thyroid containing the larger percentage of iodine had the greater effect but there were many exceptions which we are unable to explain. It would probably be impossible to detect small variations in the percentage of iodine in different thyroid preparations from their effects upon the resistance of mice to morphine.

As these experiments do not offer many points of special interest they will be reproduced in abstract only. The average loss of weight, expressed in percentage of original weight, is given in the last column.

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[a] Starvation markedly increases the resistance of animals to some poisons; this is the case, for example, with acetonitrile. (See R. Hunt, Studies in Experimental Alcoholism, Bull. 33, Hygienic Laboratory, 1907, p. 34.)

SERIES I.—SHEEP THYROID.

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of morphine in mgm. per gm.		Loss in weight in percentage of original weight.
				Recovered.	Died.	
A	0.001	0.085	0.00085	0.17	0.25	9.0
B	.001	.11	.0011	.09	.11	14.3
C	.001	.11	.0011	.12	.16	3.7
D	.001	.19	.0019	.12	.14	10.7
E	.001	.21	.0021	.13	.16	14.6
F. Controls				.19	.20	9.9

The resistance of mice to morphine was uniformly diminished by the thyroid. The thyroid having the least effect was the preparation containing the smallest percentage of iodine; the effects of the other preparations were nearly equal, although some contained nearly twice as much iodine as others. There was no constant relation between the loss of weight and the diminished resistance to morphine.

SERIES II.

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose in mgm. per gm.		Loss in weight.
				Recovered.	Died.	
A	0.005	0.085	0.00425	0.17	0.18	8.6
B	.005	.11	.0055	.08	.11	13.2
C	.005	.19	.0095	.09	.10	8.8
D	.005	.21	.0105	.07	.09	23.5
E	.01	.1	.01	.10	.12	15.1
F	.01	.11	.011	.13	.14	16.5
G	.01	.11	.011	.105	.12	13.6
H	.01	.11	.011	.13	.16	14.2
I	.01	.19	.019	.08	.09	15.0
J	.01	.21	.021	.06	.08	9.4
K. Controls				.17	.18	7.5

The thyroid with the largest percentage of iodine was the most active when the smaller (0.005 gm.) as well as when the larger (0.01 gm.) amounts of thyroid were fed. In some cases the loss of weight was parallel with the increased susceptibility to morphine; in other cases it was not.

SERIES III.

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose in mgm. per gm.		Loss in weight.[a]
				Recovered.	Died.	
A	0.01	0.05	0.005	0.18	0.22	+ 3.0
B	.01	.104	.0104	.11	.16	5.8
C	.01	.19	.0190		.09	18.0
D	.01	.298	.0298	.09	.10	11.7
E	.01	.33	.0330	.07	.09	2.4
F. Controls				.43	.45	+ 3.7

[a] The + sign indicates that the mice had increased in weight.

With the increased percentage of iodine in the thyroid there was, with one exception, a uniform increase in physiological activity, as shown by the increased susceptibility to morphine.

The changes in weight were in most cases not marked; in two instances there was a slight increase. The most marked change was with the mice of group C; the average loss of weight with these was 18 per cent. Perhaps this indicates that the mice of this series had eaten more of the cakes than had the mice of the other series.

The following series may be quoted as additional illustrations of how the susceptibility of mice to morphine may be increased by the administration of thyroid:

SERIES IV.

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mg. I in thyroid fed daily.	Fatal dose in mgm. per gm.		Loss in weight.[a]
				Recovered.	Died.	
A	0.01	0.19	0.019	0.10	0.15	5.1
B. Controls				.36		+6.8

SERIES V.

A	0.03	0.186	0.0558	0.18	0.22	14.2
B. Controls				.38	.43	7.9

SERIES VI.[a]

A	0.2	0.186	0.0372	0.07	0.08	1.9
B. Controls				.24	.24	1.5

[a] The + sign indicates that the mice had increased in weight.

[b] The experiment was continued but six days instead of ten, as was usually the case.

SUMMARY OF EXPERIMENTS ON MICE.

The above experiments show that the resistance of mice to morphine was uniformly lowered by the feeding of thyroid. This lowering of the resistance occurred independently of the changes in weight; in some cases there was a markedly increased susceptibility to morphine with an increase in weight. In general the thyroid containing the higher percentages of iodine caused the greatest changes in resistance, but there were a number of exceptions.

c.—Experiments on Guinea Pigs.

Experiments were not made in which the effects of thyroid containing different percentages of iodine upon the resistance of guinea pigs to morphine were determined. The following experiments show that the resistance of these animals to morphine is diminished by the feeding of thyroid. The amount of thyroid was very large; in the

second series there was a loss of weight, while in the first there was only a retardation of growth:

SERIES I.

A. SHEEP THYROID; 0.084 PER CENT IODINE.

Date.	Weight of pig.	Remarks.
1907.		
May 1	265	Feeding of thyroid, 0.120 gm. daily, begun.
4	265	
8	260	
10	260	
13	275	Morphine sulphate, 55 mgms., i. e., 0.2 mgm. per gm. pig. Survived.
May 1	330	Thyroid as above.
4	330	
8	320	
11	315	
15	267	Morphine sulphate, 66.75 mgms., i. e., 0.25 mgm. per gm. pig. Died 16 hours.
May 1	285	Thyroid as above.
4	280	
8	280	
11	280	
14	259	Morphine sulphate, 77.7 mgms., i. e., 0.3 mgm. per gm. pig. Died 8½ hours.
May 1	215	Thyroid as above.
4	200	
8	215	
11	215	
14	208	Morphine sulphate, 83.2 mgms., i. e., 0.4 mgm. per gm. pig. Died 3 hours.

B. CONTROLS.

1907.		
May 1	320	
4	335	
9	360	
13	385	
14	348	Morphine sulphate, 174 mgms., i. e., 0.5 mgm. per gm. pig. Survived.
May 1	200	
4	210	
9	220	
13	275	
15	250	Morphine sulphate, 150 mgms., i. e., 0.6 mgm. per gm. pig. Died 3 hours.
May 1	225	
4	240	
9	275	
13	305	Morphine sulphate, 213.5 mgms., i. e., 0.7 mgm. per gm. pig. Died 3¾ hours.

Series II.

A. SHEEP THYROID; 0.084 PER CENT IODINE.

Date.	Weight of pig.	Remarks.
1907.		
April 4	265	Feeding of thyroid, 0.24 gm. daily, begun.
8	232	
12	220	
16	195	Morphine sulphate, 48.75 mgms., i. e., 0.25 mgm. Died 10 to 15 hours.
April 4	244	Thyroid as above.
8	235	
12	255	
14	256	Morphine sulphate, 76.8 mgms., i. e., 0.3 mgm. per gm. pig. Died 21 hours.
April 4	260	Thyroid as above.
8	225	
12	215	
14	217	Morphine sulphate, 108.5 mgms., i. e., 0.5 mgm. per gm. pig. Died 4 hours.

B. CONTROLS.

1907.		
April 4	250	
8	270	
12	300	
14	302	Morphine sulphate, 196.3 mgms., i. e., 0.65 mgm. per gm. pig. Survived.
April 4	252	
8	280	
12	315	
15	335	Morphine sulphate, 251.25 mgms., i. e., 0.75 mgm. per gm. pig. Died 3½ hours.
April 4	240	
8	275	
12	290	
14	307	Morphine sulphate, 245.6 mgms., i. e., 0.8 mgm. Died 2 hours.

Summary. The results of the above experiments may be summarized as follows:

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose in mgm. per gm.		Average loss of weight in per cent of original weight.[a]
				Recovered.	Died.	
Series I	0.12	0.084	0.1008	0.2	0.25	7.9
Controls				.5	.60	+21.2
Series II	.24	.084	.2016		.25	13.1
Controls				.65	.75	+27.2

[a] The + sign indicates that the guinea-pigs had increased in weight.

The guinea pigs which had received the thyroid died from one-third to one-half of the dose of morphine fatal to the controls. The amount of thyroid fed was very large and the animals were evidently deeply intoxicated.

Conclusions from the experiments with morphine.

The resistance of rats, mice, and guinea pigs to morphine is uniformly lowered by the feeding of thyroid. This occurs independently of any effect the thyroid may have upon the weight of the animals. In the case of the rat there is a close parallelism between the physiological effect of the thyroid, as determined by the increased susceptibility to morphine, and the percentage of iodine. A similar parallelism was found, in general, in the experiments on mice; the animals which had received thyroid with a higher percentage of iodine almost invariably died from a smaller dose of morphine than did those which had received thyroid with a low percentage of iodine. The question of the relation between the iodine content and the physiological activity of the thyroid was not tested on guinea pigs. The results of the experiments with morphine on rats and mice are therefore an additional argument for the view that the degree of physiological activity of thyroid is parallel to the iodine content.

We have no explanation to offer for the effect of thyroid feeding upon the resistance of animals to morphine further than the suggestion made by one of us in a previous paper:[a]

> I have not been able to determine the cause of this increased susceptibility; possibly the thyroid, which is known to hasten the oxidation of fats, affects the lipoids of the nervous system in such a manner that poisons, such as morphine, gain access to it more easily.

Mansfeld[b] found that rabbits which had been deprived of food for a few days were much more susceptible to morphine than were normal rabbits; he endeavored to explain this in the terms of the Meyer-Overton theory of narcosis: In starvation there is a diminution of fat in the body, except in the central nervous system; as a result of this a larger proportion of the fat soluble narcotic is taken up by the nervous system, and so is able to exert a greater toxic action. Although thyroid has a tendency to cause a diminution of fat in the body, we do not believe that this can have played a large part in our experiments; in some of these the thyroid had increased the susceptibility of the animals to morphine ten times without causing any change in weight.

These experiments may have some bearing upon the use of morphine in exophthalmic goiter (hyperthyroidism). There seems to be unanimity of opinion among clinicians that general anæsthetics are very dangerous in this condition.[c] The opinions differ as to the us-

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[a] R. Hunt, J. Am. M. Ass., Chicago, 1907, **49,** p. 1325.

[b] G. Mansfeld, Arch. internat. de pharmacodynamie et de thérapie, 1905, **15,** p. 467.

[c] *cf.* Th. Kocher, Verhandl. d. deutsch. Gesellsch. f. Chir., Berl., 1901, 30te Kong. p. 346; A. Kocher, Mitt. a. d. Grenzgeb. d. Med. u. Chir., Jena, 1902, **9,** p. 1. Angerer (Münch. m. Wchschr., 1896, **43,** p. 71) states that the feeding of thyroid to patients with goiter renders them especially liable to heart failure when a general anæsthetic is administered.

of morphine or opium. Thus Tyson[a] considers opium to be a rational remedy, although he states that Ord and MacKenzie found that it is not well borne; Tyson prefers codeine. Our experiments showed that morphine is very toxic to animals in which a condition of thyroidism has been produced. Of course it has not been conclusively proved that there is a condition of hyperthyroidism in exophthalmic goiter or that man would react to morphine in the same way as do the lower animals. If we may judge of the degree of thyroidism from the loss of weight, our animals were as a rule certainly less deeply intoxicated than are many patients with exophthalmic goiter.

The increased susceptibility to morphine of animals to which thyroid has been fed is suggestive in another connection.

May not many of the very diverse symptoms which occur in exophthalmic goiter be secondary, i. e., may not the condition of hyperthyroidism render many of the organs abnormally sensitive to poisons originating in the body itself (possibly products of intestinal putrefaction) or introduced from without (substances contained in meat, for example)? Organs rendered hypersensitive by the thyroid secretion may respond to amounts of such poisons ordinarily too small to produce any symptoms, just as the thyroid-fed rats may die from doses of morphine which would ordinarily be entirely innocuous.

As is well known there are few diseases in which so many drugs and forms of treatment have been recommended, often apparently with good reason, as in the case of exophthalmic goiter. Perhaps the effect of these is entirely secondary, i. e., some intestinal antiseptics[b] may check the formation of injurious substances, others may diminish the irritability of an over-stimulated organ.

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[a] J. Tyson, Internat. Clin., Phila., 1906, Series 16, **1,** p. 3.

[b] *cf.* W. H. Thomson, Am. J. Med. Sci., 1908, **135,** p. 313.

Part II.

ON THE NATURE OF THE RELATION BETWEEN THE IODINE PERCENTAGE AND THE PHYSIOLOGICAL ACTIVITY OF THYROID.

It has been shown above that there is almost invariably a parallelism between the iodine content of thyroid and its physiological activity. The nature of this relation may now be discussed. Some of the writers who recognize that there is such a parallelism hold that the larger amount of iodine in the more active thyroid is a result and not the cause of the greater activity. In other words, according to this view, the more active the gland the larger the amount of iodine with which its substance can combine.[a]

The arguments advanced for this theory are in part the same as those which have been urged against the view that the iodine is an important constituent of the thyroid and which have been discussed above. Such arguments are based largely upon what may be called statistical studies, and, as we have already seen, conclusions drawn from such studies do not necessarily apply to the thyroid when used as a drug. Moreover, were this view correct, we should expect to find at times thyroid poor in iodine but with a high degree of physiological activity, for the amount of iodine present in the thyroid is to a considerable extent accidental, being dependent upon the amount of this element available in the food. We have, however, never found a specimen of thyroid with a low percentage of iodine and with a high degree of physiological activity. Whether from the same or from widely separated species, the activity was in general parallel with the iodine content.

A stronger argument against the view that the activity of thyroid is independent of the percentage of iodine is found in a metabolism experiment of Roos,[b] in which the activity of normal thyroid was compared with that of thyroid which had combined with a larger amount of iodine *in vivo*. Roos found the iodine-free thyroid of a dog to be without appreciable effect upon nitrogen excretion, whereas an equal amount of thyroid from a dog which had received 20 grams of potassium iodide in eighteen days and which contained 0.35 per cent iodine had a very distinct effect. Only one experiment was performed, and the result, although distinct, was not very marked.[c]

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[a] *cf.* S. J. Meltzer, N. Yorker med. Monatschr., 1907, **19**, p. 223.

[b] E. Roos, Ztschr. f. physiol. Chem., Strassb., 1899, **28**, p. 47.

[c] *cf.* F. Blum, Verhandl. d. Kong. f. inn. Med., 1906, **23**, p. 196.

Moreover, the evidence is far from conclusive that there may not have been differences between the two thyroid preparations other than that of the iodine content. There is also the possibility to be considered that the potassium iodide that was administered during the course of eighteen days had in some way simply stimulated the thyroid to an increased production of an active substance and that this active substance secondarily retained an additional amount of iodine and that the increased activity of the gland was due to the former and not to the latter.

It seemed to us that the following conditions should be fulfilled in order to make an experiment of this character conclusive: There should be evidence that the thyroid of the animals which received the iodine compound was, before its administration, in approximately the same condition as those which were to serve as controls; and, in the second place, the iodine should be administered for but a short time, so as to exclude any prolonged stimulating action. We endeavored to meet these conditions as follows: The thyroids of several groups of ten dogs each were analyzed for iodine, so as to obtain data as to the usual percentage of iodine present. To similar groups of ten dogs two doses of potassium iodide or of iodoform were given on successive days and the dogs killed on the third or fourth day. It was found that a large amount of iodine was taken up by the thyroid and that the latter, tested by our methods, showed greatly increased activity. Moreover, the increased activity was in direct proportion to the amount of iodine which had been taken up by the thyroid. We believe the conclusion is justified that the physiological activity of the thyroid from the different groups of dogs was approximately the same before the iodine was given, and therefore the increased activity of the thyroid of the iodine-fed dogs must have been due entirely to the iodine absorbed. The increased activity appeared much too rapidly to permit of the supposition that the iodine had simply accelerated the production of a more powerful substance independent of the iodine. The experiments were as follows:

SERIES A.

Forty-six dogs were divided into five groups. There were ten animals in each of the first three groups, seven in the fourth, and nine in the fifth. To each of the dogs of the fourth group from 1.5 to 2 grams of potassium iodide were given *per os;* they were killed twenty-four hours later. Each of the dogs of the fifth group received 1 to 1.3 grams iodoform in capsules; this was repeated on the following day and the dogs killed on the third day. The thyroids from all these dogs were weighed, ground up finely, dried at 50° C. and again weighed, and the iodine determined.

Group.	Weight of thyroid fresh.	Weight of thyroid dried.	Per cent of water.	Per cent of iodine.
1	18.03	4.84	73.15	0.129
2	25.67	6.86	73.27	.111
3	14.09	3.99	71.68	.106
4 (fed KI)	13.25	3.35	74.71	.148
5 (fed CHI_3)	25.92	7.22	72.14	.30

The glands of the controls contained from 0.106 to 0.129 per cent iodine; those which had received the potassium iodide had 0.148 and those which had received the iodoform 0.3 per cent. The glands of all five series lost approximately the same per cent of moisture on drying; this is additional evidence that they are strictly comparable.

The following experiments were performed with these preparations:

1. EXPERIMENTS WITH ACETONITRILE.

a. Experiments on Mice.

Series I.

A. THYROID OF GROUP 2 (NORMAL); 0.111 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1907.		
June 5	12.05	Feeding of cakes each containing 0.0025 gms. thyroid commenced.
8	12.92	
11	12.92	
15	13.07	
16	12.63	Acetonitrile, 15.16 mgms., i. e., 1.2 mgms. per gm. mouse. Survived.
June 5	10.73	Thyroid as above.
8	11.07	
11	10.85	
15	10.50	
16	10.75	Acetonitrile, 15.05 mgms., i. e., 1.4 mgms. per gm. mouse. Survived.
June 5	12.95	Thyroid as above.
8	13.42	
11	11.77	
15	10.41	Acetonitrile, 16.66 mgms., i. e., 1.6 mgms. per gm. mouse. Died 3 hours.
June 5	14.22	Thyroid as above.
8	13.82	
11	13.00	
15	11.60	Acetonitrile, 23.2 mgms., i. e., 2 mgms. per gm. mouse. Died 1 hour.

B. THYROID OF GROUP 4 (POTASSIUM IODIDE); 0.148 PER CENT IODINE.

1907.		
June 5	11.06	Feeding of cakes each containing 0.0025 gm. thyroid commenced.
8	12.27	
11	12.35	
15	12.00	Acetonitrile, 19.2 mgms., i. e., 1.6 mgms. per gm. mouse. Survived.
June 5	11.64	Thyroid as above.
8	11.52	
11	11.52	
15	12.15	
16	11.80	Acetonitrile, 22.42 mgms., i. e., 1.9 mgms. per gm. mouse. Died 1¼ hours.
June 5	12.74	Thyroid as above.
8	12.02	
11	11.62	
15	11.11	
16	10.94	Acetonitrile, 24.07 mgms.. i. e., 2.2 mgms. per gm. mouse. Died 3¼ hours.

C. THYROID OF GROUP 5 (IODOFORM); 0.3 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1907.		
June 5	12.52	Feeding of cakes each containing 0.0025 gm. thyroid commenced.
8	13.70	
11	13.20	
14	12.89	Acetonitrile, 18.05 mgms., i. e., 1.4 mgms. per gm. mouse. Survived.
June 5	14.01	Thyroid as above.
8	14.90	
11	13.70	
15	12.30	Acetonitrile, 22.14 mgms., i. e., 1.8 mgms. per gm. mouse. Survived.
June 5	13.30	Thyroid as above.
8	13.13	
11	13.20	
15	12.18	
16	12.10	Acetonitrile, 30.25 mgms., i. e., 2.5 mgms. per gm. mouse. Survived.
June 5	11.79	Thyroid as above.
8	11.83	
11	11.40	
15	10.18	
16	9.23	
17	8.71	Acetonitrile, 24.39 mgms., i. e., 2.8 mgms. per gm. mouse. Died 2 hours.

D. CONTROLS.

1907.		
June 5	12.48	Feeding of cakes without thyroid commenced.
8	13.61	
11	13.42	
15	12.96	Acetonitrile, 4.28 mgms., i. e., 0.33 mgm. per gm. mouse. Survived.
June 5	8.23	Cakes as above.
8	7.56	
11	8.07	
14	8.05	Acetonitrile, 2.98 mgms., i. e., 0.37 mgm. per gm. mouse. Survived.
June 5	12.10	Cakes as above.
8	13.16	
11	12.97	
14	13.00	Acetonitrile, 5.2 mgms., i. e., 0.4 mgm. per gm. mouse. Died about 2 hours.
June 5	12.30	Cakes as above.
8	11.83	
11	12.57	
15	12.66	
16	12.22	Acetonitrile, 4.89 mgms., i. e., 0.4 mgm. per gm. mouse. Died 2 hours.

Summary.—The results of the above experiments may be tabulated as follows:

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of acetonitrile in mgms per gm.	
				Recovered.	Died.
A	0.0025	0.111	0.0027	1.4	1.6
B	.0025	.148	.0037	1.6	1.9
C	.0025	.300	.0075	2.5	2.8
D. Controls				.37	.4

From the above experiments it is seen that there is a direct parallelism between the per cent of iodine and the physiological activity of the thyroid. The thyroid of Group 5 (C) (from the dogs which had received iodoform and which contained 0.3 per cent iodine) enabled the mice to recover from about twice as much acetonitrile as did that from Group 2 (A) (normal, 0.111 per cent iodine). The thyroid of Group 4 (B) (potassium iodide fed dogs; 0.148 per cent iodine) was slightly more active than that of Group 2 and less active than that of Group 5. The amount of thyroid fed was comparatively large, and in the case of Group 5 was probably greater than the minimum amount necessary to produce the maximum effect.

Series II.

In the following experiments different amounts of the thyroid were fed; in the first three the amounts were selected so as to make the total iodine about the same in all.

A. THYROID OF GROUP 3 (NORMAL); 0.106 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
April 14	15.30	Feeding of cakes each containing 0.003 gm. thyroid commenced.
17	16.02	
20	16.37	
22	15.99	Acetonitrile, 34.38 mgms., i. e., 2.15 mgms. per gm. mouse. Survived.
April 14	21.60	Thyroid as above.
17	21.64	
20	21.34	
22	22.10	
23	22.03	Acetonitrile, 55.08 mgms., i. e., 2.5 mgms. per gm. mouse. Survived.
April 14	23.58	Thyroid as above.
17	24.74	
20	24.64	
23	25.05	Acetonitrile, 67.64 mgms., i. e., 2.7 mgms. per gm. mouse. Died one-half hour.
April 14	27.56	Thyroid as above.
17	27.72	
20	27.50	
23	28.30	Acetonitrile, 89.9 mgms., i. e., 3 mgms. per gm. mouse. Died 2 hours.

B. THYROID OF GROUP 4 (POTASSIUM IODIDE); 0.148 PER CENT IODINE.

1908.		
April 14	24.70	Feeding of cakes each containing 0.002 gm. thyroid commenced.
17	23.62	
20	23.57	
22	22.70	Acetonitrile, 56.75 mgms., i. e., 2.5 mgms. per gm. mouse. Survived.
April 14	19.12	Thyroid as above.
17	19.58	
20	19.68	
23	19.52	Acetonitrile, 50.75 mgms., i. e., 2.6 mgms. per gm. mouse. Survived.
April 14	15.10	Thyroid as above.
17	16.14	
20	16.14	
23	15.82	Acetonitrile, 45.88 mgms., i. e., 2.9 mgms. per gm. mouse. Survived.
April 14	22.72	Thyroid as above.
17	24.32	
20	24.92	
22	25.32	
23	25.50	Acetonitrile, 73.95 mgms., i. e., 2.9 mgms. per gm. mouse. Died 1½ hours.

C. THYROID OF GROUP 5 (IODOFORM); 0.3 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
April 14	22.95	Feeding of cakes each containing 0.001 gm. thyroid commenced.
17	22.64	
20	22.20	
22	23.02	Acetonitrile, 46.04 mgms., i. e., 2 mgms. per gm. mouse. Survived.
April 14	13.76	Thyroid as above.
17	14.03	
20	12.58	
23	12.50	Acetonitrile, 37.5 mgms., i. e., 3 mgms. per gm. mouse. Survived.
April 14	16.66	Thyroid as above.
17	17.24	
20	17.49	
23	17.70	Acetonitrile, 51.33 mgms., i. e., 2.9 mgms. per gm. mouse. Died 2½ hours.
April 14	24.36	Thyroid as above.
17	23.27	
20	23.52	
22	24.03	
23	23.36	Acetonitrile, 74.75 mgms., i. e., 3.2 mgms. per gm. mouse. Died one-half hour.

D. THYROID OF GROUP 5 (IODOFORM); 0.3 PER CENT IODINE.

1908.		
April 14	19.36	Feeding of cakes each containing 0.002 gm. thyroid commenced.
17	19.70	
20	20.26	
22	20.74	Acetonitrile, 67.4 mgms., i. e., 3.25 mgms. per gm. mouse. Survived.
April 14	17.75	Thyroid as above.
17	18.85	
20	18.57	
22	18.42	
23	18.44	Acetonitrile, 73.76 mgms., i. e., 4 mgms. per gm. mouse. Survived.
April 14	14.94	Thyroid as above.
17	15.36	
20	15.28	
23	15.33	Acetonitrile, 67.45 mgms., i. e., 4.4 mgms. per gm. mouse. Survived.
April 14	24.09	Thyroid as above.
17	26.07	
20	25.45	
23	25.33	
24	25.15	Acetonitrile, 125.75 mgms., i. e., 5 mgms. per gm. mouse. Died 2 hours.

E. CONTROLS.

1908.		
April 14	17.56	Feeding of cakes without thyroid commenced.
17	17.76	
20	16.42	
23	16.71	Acetonitrile, 10.86 mgms., i. e., 0.65 mgm. per gm. mouse. Survived.
April 14	27.94	Cakes as above.
17	28.76	
20	28.58	
23	27.83	Acetonitrile, 19.94 mgms., i. e., 0.72 mgm. per gm. mouse. Survived.
April 14	19.90	Cakes as above.
17	19.62	
20	19.34	
22	19.90	
23	19.44	Acetonitrile, 14.58 mgms., i. e., 0.75 mgm. per gm. mouse. Died 2 hours.
April 14	23.54	Cakes as above.
17	23.86	
20	23.92	
23	23.54	
24	23.04	Acetonitrile, 17.74 mgms., i. e., 0.77 mgm. per gm. mouse. Died 1¾ hours.

Summary.—The results of the foregoing experiments may be tabulated as follows:

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.003	0.106	0.00318	2.5	2.7
B	.002	.148	.00296	2.9	2.9
C	.001	.300	.0030	3.0	2.9
D	.002	.300	.0060	4.4	5.0
E. Controls				.72	.75

Thyroid containing 0.106, 0.148, and 0.3 per cent iodine, respectively, was fed to mice. When fed in amounts corresponding to the ratio of 3, 2, and 1 (namely, in the inverse ratio to the iodine content) the physiological effects were approximately equal. With equal amounts of the thyroid containing 0.148 and 0.3 per cent iodine the latter was much the more active.

Series III.

In the following experiments the effects of the thyroid of Group 3 (normal; 0.106 per cent iodine) and of Group 5 (iodoform fed dogs; 0.3 per cent iodine) were compared.

A. THYROID OF GROUP 3 (NORMAL); 0.106 PER CENT IODINE.

Date.	Weight.	Remarks.
1908.		
April 25	18.45	Feeding of cakes each containing 0.0005 gm. thyroid commenced.
29	19.74	
May 2	19.74	
3	19.74	Acetonitrile, 35.53 mgms., i. e., 1.8 mgms. per gm. mouse. Survived.
April 25	15.00	Thyroid as above.
29	15.16	
May 2	15.14	
4	15.28	
5		Acetonitrile, 29.03 mgms., i. e., 1.9 mgms. per gm. mouse. Survived.
April 25	15.73	Thyroid as above.
29	14.88	
May 2	14.50	
4	14.34	Acetonitrile, 30.11 mgms., i. e., 2.1 mgms. per gm. mouse. Died 6 hours.
April 25	16.87	Thyroid as above.
29	18.20	
May 2	17.60	
4	18.15	Acetonitrile, 41.75 mgms., i. e., 2.3 mgms. per gm. mouse. Died 3½ hours.

B. THYROID OF GROUP 3 (NORMAL); 0.106 PER CENT IODINE.

Date.	Weight.	Remarks.
1908.		
April 25	13.75	Feeding of cakes each containing 0.0015 gm. thyroid commenced.
29	14.34	
May 2	14.92	
3	14.92	Acetonitrile, 37.3 mgms., i. e., 2.5 mgms. per gm. mouse. Survived.
April 25	14.20	Thyroid as above.
29	14.30	
May 2	13.48	
4	13.28	Acetonitrile, 41.17 mgms., i. e., 3.1 mgms. per gm. mouse. Survived.
April 25	16.32	Thyroid as above.
29	15.28	
May 2	15.32	
4	14.68	
5	.....	Acetonitrile, 52.85 mgms., i. e., 3.6 mgms. per gm. mouse. Died 1½ hours.
April 25	16.23	Thyroid as above.
29	17.68	
May 2	17.34	
4	16.28	Acetonitrile, 61.86 mgms., i. e., 3.8 mgms. per gm. mouse. Died 50 hours.

C. THYROID OF GROUP 5 (IODOFORM FED DOGS); 0.3 PER CENT IODINE.

1908.		
April 25	14.93	Feeding of cakes each containing 0.0005 gm. thyroid commenced.
29	16.50	
May 2	16.84	
3	16.84	Acetonitrile, 45.47 mgms., i. e., 2.7 mgms. per gm. mouse. Survived.
April 25	15.99	Thyroid as above.
29	16.64	
May 2	16.32	
4	16.54	Acetonitrile, 51.27 mgms., i. e., 3.1 mgms. per gm. mouse. Survived.
April 25	15.49	Thyroid as above.
29	16.37	
May 2	12.96	
4	14.25	Acetonitrile, 52.72 mgms., i. e., 3.7 mgms. per gm. mouse. Survived.
April 25	15.13	Thyroid as above.
29	15.64	
May 2	14.75	
4	14.72	
5	.....	Acetonitrile, 61.82 mgms., i. e., 4.2 mgms. per gm. mouse. Died 1½ hours.

D. THYROID OF GROUP 5.

1908.		
April 25	15.05	Feeding of cakes each containing 0.001 gm. thyroid commenced.
29	16.08	
May 2	15.66	
3	15.66	Acetonitrile, 46.98 mgms., i. e., 3 mgms. per gm. mouse. Survived.
April 25	14.84	Thyroid as above.
29	15.44	
May 2	14.24	
4	14.15	Acetonitrile, 50.94 mgms., i. e., 3.6 mgms. per gm. mouse. Survived
April 25	15.24	Thyroid as above.
29	15.00	
May 2	14.83	
4	14.69	Acetonitrile, 60.23 mgms., i. e., 4.1 mgms. per gm. mouse. Survived.
April 25	15.54	Thyroid as above.
29	16.04	
May 2	16.16	
4	15.80	
5	.....	Acetonitrile, 74.26 mgms., i. e., 4.7 mgms. per gm. mouse. Died 4½ hours.

E. CONTROLS.

Date.	Weight.	Remarks.
1908.		
April 25	13.45	Feeding of cakes without thyroid commenced.
29	14.47	
May 2	14.56	
3	14.56	Acetonitrile, 7.43 mgms., i. e., 0.51 mgm. per gm. mouse. Survived.
April 25	18.43	Cakes as above.
29	19.67	
May 2	19.76	
4	19.54	
5		Acetonitrile, 10.16 mgms., i. e., 0.52 mgm. per gm. mouse. Died 1 hour.
April 25	16.88	Cakes as above.
29	15.43	
May 2	15.57	
4	15.21	
5		Acetonitrile, 8.06 mgms., i. e., 0.53 mgm. per gm. mouse. Died 8 hours.

Summary.—The results of the above experiments may be tabulated as follows:

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.0005	0.106	0.00053	1.9	2.1
B	.0015	.106	.00159	3.1	3.6
C	.0005	.300	.00150	3.7	4.2
D	.001	.300	.00300	4.1	4.7
E. Controls				.51	.52

With equal amounts of thyroid containing, respectively, 0.106 and 0.3 per cent iodine, the effect of the latter was much greater than that of the former; with three parts of the former and one part of the latter the effects were nearly equal. One part of the thyroid rich in iodine was also much more active than one and one-half parts of the thyroid poor in iodine.

SERIES IV.

In this series equal amounts of the thyroid of Groups 2 and 1 (normal) and of Group 5 (iodoform fed dogs) were compared.

A. THYROID OF GROUP 2 (NORMAL); 0.111 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
May 9	13.83	Feeding of cakes, each containing 0.0005 gm. thyroid, commenced.
16	12.49	
18	11.76	Acetonitrile, 12.94 mgms., i. e., 1.1 mgms. per gm. mouse. Survived.
May 9	18.52	Thyroid as above.
16	18.43	
18	18.29	Acetonitrile, 26.61 mgms., i. e., 1.4 mgms. per gm. mouse. Died 5 hours.
May 9	18.48	Thyroid as above.
16	19.00	
17	.....	Acetonitrile, 34.2 mgms., i. e., 1.8 mgms. per gm. mouse. Died 2 hours.
May 9	14.98	Thyroid as above.
16	12.80	
17	.....	Acetonitrile, 32.0 mgms., i. e., 2.5 mgms. per gm. mouse. Died 3 hours.

B. THYROID OF GROUP 1 (NORMAL); 0.129 PER CENT IODINE.

1908.		
May 9	16.17	Feeding of cakes, each containing 0.0005 gm. thyroid, commenced.
15	16.84	
18	16.71	Acetonitrile, 26.74 mgms., i. e., 1.6 mgms. per gm. mouse. Survived.
May 9	11.50	Thyroid as above.
15	12.67	
16	12.46	
18	12.59	Acetonitrile, 22.62 mgms., i. e., 1.8 mgms. per gm. mouse. Survived.
May 9	15.87	Thyroid as above.
15	15.17	
16	14.87	
17	.....	Acetonitrile, 31.23 mgms., i. e., 2.1 mgms. per gm. mouse. Died 1¼ hours.
May 9	15.71	Thyroid as above.
15	14.61	
16	14.58	
17	.....	Acetonitrile, 36.45 mgms., i. e., 2.5 mgms. per gm. mouse. Died 1½ hours.

C. THYROID OF GROUP 5 (IODOFORM); 0.3 PER CENT IODINE.

1908.		
May 9	21.46	Feeding of cakes, each containing 0.0005 gm. thyroid, commenced.
16	19.13	
18	19.15	Acetonitrile, 55.54 mgms., i. e., 2.9 mgms. per gm. mouse. Survived.
May 9	14.50	Thyroid as above.
16	13.39	
17	.....	Acetonitrile, 41.51 mgms., i. e., 3.1 mgms. per gm. mouse. Survived..
May 9	16.12	Thyroid as above.
16	15.02	
18	15.05	Acetonitrile, 49.66 mgms., i. e., 3.3 mgms. per gm. mouse. Died 2½ hours.
May 9	14.26	Thyroid as above.
16	12.25	Acetonitrile, 42.88 mgms., i. e., 3.5 mgms. per gm. mouse. Died 4⅓ hours.

D. (CONTROLS.)

Date.	Weight of mouse.	Remarks.
1908.		
May 9	16.65	Feeding of cakes without thyroid commenced.
15	16.06	
16	16.05	
17		Acetonitrile, 5.78 mgms., i. e., 0.36 mgm. per gm. mouse. Survived.
May 9	16.50	Cakes as above.
15	15.74	
16	15.42	
18	15.56	Acetonitrile, 5.76 mgms., i. e., 0.37 mgm. per gm. mouse. Died 2 hours.
May 9	15.79	Cakes as above.
15	11.80	
16	12.15	
18	13.16	Acetonitrile, 5.27 mgms., i. e. 0.4 mgm. per gm. mouse. Died 4 hours.

Summary.—The results of the above experiments may be summarized as follows:

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.0005	0.111	0.00055	1.1	1.4
B	.0005	.129	.00064	1.8	2.1
C	.0005	.300	.00150	3.1	3.3
D. Controls				.36	.37

The thyroid of the dogs which had received iodoform was much more active than that of the normal dogs.

b. Experiments on Rats.

Results very similar to the above were obtained in a series of experiments upon rats. In these animals there is a diminution of resistance to acetonitrile.

A. THYROID OF GROUP 2 (NORMAL); 0.111 PER CENT IODINE.

Date.	Weight of rat.	Remarks.
1908.		
May 15	32	Feeding of cakes, each containing 0.0005 gm. thyroid, commenced.
18	33	
20	33	
23	32	Acetonitrile, 51.2 mgms., i. e., 1.6 mgms. per gm. rat. Died about 17 hours.
May 15	43	Thyroid as above.
18	43	
20	43	
23	41	
24		Acetonitrile, 73.8 mgms., i. e., 1.8 mgms. per gm. rat. Survived.
May 15	50	Thyroid as above.
18	50	
20	49	
23	48	Acetonitrile, 100.8 mgms., i. e., 2.1 mgms. per gm. rat. Died 2 hours.
May 15	35	Thyroid as above.
18	34	
20	34	
23	32	
25	32	Acetonitrile, 70.4 mgms., i. e., 2.2 mgms. per gm. rat. Died 4 hours.

B. THYROID OF GROUP 3 (IODOFORM); 0.3 PER CENT IODINE.

Date.	Weight of rat.	Remarks.
1908.		
May 15	36	Feeding of cakes, each containing 0.0005 gm. thyroid, commenced.
18	37	
20	37	
23	34	Acetonitrile, 34 mgms., i. e., 1 mgm. per gm. rat. Survived.
May 15	44	Thyroid as above.
18	42	
20	43	
23	41	
24	41	Acetonitrile, 53.3 mgms., i. e., 1.3 mgms. per gm. rat. Survived.
May 15	38	Thyroid as above.
18	37	
20	36	
23	35	Acetonitrile, 52.5 mgms., i. e., 1.5 mgms. per gm. rat. Died 1½ hours.

C. THYROID OF GROUP 2 (NORMAL); 0.111 PER CENT IODINE.

1908.		
May 15	41	Feeding of cakes, each containing 0.0015 gm. thyroid, commenced.
18	39	
20	38	
23	38	Acetonitrile, 45.6 mgms., i. e., 1.2 mgms. per gm. rat. Survived.
May 15	43	Thyroid as above.
18	41	
20	41	
23	38	
24		Acetonitrile, 49.4 mgms., i. e., 1.3 mgms. per gm. rat. Died 1 hour.
May 15	36	Thyroid as above.
18	35	
20	34	
23	33	
24		Acetonitrile, 46.2 mgms., i. e., 1.4 mgms. per gm. rat. Died 4 to 7 hours.
May 15	64	Thyroid as above.
18	57	
20	59	
23	58	Acetonitrile, 92.8 mgms., i. e., 1.6 mgms. per gm. rat. Died 3 hours.

D. THYROID OF GROUP 2 (NORMAL); 0.111 PER CENT IODINE.

1908.		
May 15	38	Feeding of cakes, each containing 0.003 gm. thyroid, commenced.
18	37	
20	36	
23	35	Acetonitrile, 28 mgms., i. e., 0.8 mgm. per gm. rat. Survived.
May 15	45	Thyroid as above.
18	43	
20	43	
23	41	
24	41	Acetonitrile 36.9 mgms., i. e., 0.9 mgm. per gm. rat. Survived.
May 15	37	Thyroid as above.
18	35	
20	37	
23	34	
24		Acetonitrile, 34 mgms., i. e., 1 mgm. per gm. rat. Died 1 hour.
May 15	31	Thyroid as above.
18	31	
20	31	
23	29	Acetonitrile, 31.9 mgms., i. e., 1.1 mgms. per gm. rat. Died 2½ hours.

E. THYROID OF GROUP 5 (IODOFORM); 0.3 PER CENT IODINE.

Date.	Weight of rat.	Remarks.
1908.		
May 15	43	Feeding of cakes, each containing 0.001 gm. thyroid, commenced.
18	36	
20	37	
23	36	
24	36	Acetonitrile, 18 mgms., i. e., 0.5 mgm. per gm. rat. Survived.
May 15	38	Thyroid as above.
18	37	
20	38	
23	35	
24	.....	Acetonitrile, 21 mgms., i. e., 0.6 mgm. per gm. rat. Died 1 to 2 hours.
May 15	36	Thyroid as above.
18	34	
20	35	
23	33	Acetonitrile, 23.1 mgms., i. e., 0.7 mgm. per gm. rat. Died 4½ hours.
May 15	41	Thyroid as above.
18	38	
20	38	
23	35	Acetonitrile, 35 mgms., i. e., 1 mgm. per gm. rat. Died 2¼ hours.

F. CONTROLS.

1908.		
May 15	41	Feeding of cakes without thyroid commenced.
18	38	
20	37	
23	38	Acetonitrile, 87.4 mgms., i. e., 2.3 mgms. per gm. rat. Survived.
May 15	41	Cakes as above.
18	39	
20	37	
23	36	Acetonitrile, 100.8 mgms., i. e., 2.8 mgms. per gm. rat. Survived.
May 15	50	Cakes as above.
18	46	
20	48	
23	44	
24	.....	Acetonitrile, 127.6 mgms. i. e., 2.9 mgms. per gm. rat. Survived.
May 15	69	Cakes as above.
18	64	
20	65	
23	62	
24	.....	Acetonitrile, 186 mgms., i. e., 3 mgms. per gm. rat. Died 2½ hours.
May 15	42	Cakes as above.
18	38	
20	38	
23	37	Acetonitrile, 114.7 mgms., i. e., 3.1 mgms. per gm. rat. Died 3 to 6 hours.

Summary.—The results of the above experiments may be tabulated as follows:

	Gm. thyroid in each cake.	Percentage of iodine in thyroid.	Mm. I in thyroid of each cake.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.0005	0.111	0.00055	1.8	2.1
B	.0005	.300	.00150	1.3	1.5
C	.0015	.111	.00166	1.2	1.3
D	.003	.111	.00333	.9	1.0
E	.001	.300	.00300	.5	.6
F. Controls	.....	.....	.....	2.9	3.0

With equal amounts of thyroid that containing the higher percentage of iodine was the more active. To obtain approximately equal effects it was necessary to give three times as much of the thyroid poor in iodine as of the thyroid rich in iodine.

2. EXPERIMENTS WITH MORPHINE.

a. Experiments on Mice.

Only one short series of experiments was performed in which the effect of feeding the above thyroid preparations upon the resistance of mice to morphine sulphate was tested.

The results indicate that the thyroid of the iodoform-fed dogs is distinctly more active in lowering the resistance of mice to morphine than is that of the normal dogs.

A. THYROID OF GROUP 2 (NORMAL); 0.111 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1907.		
July 3	11.64	Feeding of cakes, each containing 0.01 gm. thyroid, commenced.
8	11.74	
11	11.10	
13	10.40	Morphine sulphate, 0.73 mgms., i. e., 0.07 mgm. per gm. mouse. Survived
July 3	13.33	Thyroid as above.
8	13.64	
11	14.45	
14	13.33	Morphine sulphate, 1.47 mgms., i. e., 0.11 mgm. per gm. mouse. Survived.
July 3	12.14	Thyroid as above.
8	12.77	
11	12.05	
13	11.25	Morphine sulphate, 1.8 mgms., i. e., 0.16 mgm. per gm. mouse. Died three-fourths hour.

B. THYROID OF GROUP 5 (IODOFORM); 0.3 PER CENT IODINE.

1907.		
July 3	14.65	Feeding of cakes, each containing 0.01 gm. thyroid, commenced.
8	16.22	
12	13.00	
14	11.76	Morphine sulphate, 0.82 mgm., i. e., 0.07 mgm. per gm. mouse. Survived.
July 3	12.92	Thyroid as above.
8	13.02	
12	13.32	
14	11.94	Morphine sulphate, 1.07 mgms., i. e., 0.09 mgm. per gm. mouse. Survived.
July 3	13.23	Thyroid as above.
8	13.10	
12	12.45	
13	12.32	Morphine sulphate, 1.23 mgms., i. e., 0.1 mgm. per gm. mouse. Died 2 hours

C. CONTROLS.

Date.	Weight of mouse.	Remarks.
1907.		
July 3	13.30	Feeding of cakes without thyroid commenced.
8	14.40	
12	14.25	Morphine sulphate, 5.27 mgms., i. e., 0.37 mgm. per gm. mouse. Survived.
July 3	11.40	Cakes as above.
8	11.90	
12	12.45	
13	12.33	Morphine sulphate, 5.18 mgms., i. e., 0.42 mgm. per gm. mouse. Survived.
July 3	14.25	Cakes as above.
8	14.46	
12	14.85	
14	14.40	Morphine sulphate, 6.19 mgms., i. e., 0.43 mgm. per gm. mouse. Survived.
July 3	12.90	Cakes as above.
8	15.32	
12	15.72	
15	15.40	Morphine sulphate, 6.93 mgms., i. e., 0.45 mgm. per gm. mouse. Died 1¼ hours
July 3	13.85	Cakes as above.
8	12.90	
12	11.77	
14	11.75	Morphine sulphate, 5.4 mgms., i. e., 0.46 mgm. per gm. mouse. Died about 2 hours.

Summary.—The results of these experiments may be tabulated as follows:

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mg. I in thyroid fed daily.	Fatal dose of morphine sulphate in mgm. per gm.	
				Recovered.	Died.
A	0.01	0.111	0.0111	0.11	0.16
B	.01	.300	.0300	.09	.10
C. Controls				.43	.45

b. Experiments on Rats.

The following series of experiments on rats, although very incomplete, show that the activity of the thyroid, the iodine content of which has been increased by the administration of iodoform to dogs, was much greater than that of normal thyroid.

Series I.

A. THYROID OF GROUP 2 (NORMAL); 0.111 PER CENT IODINE.

Date.	Weight of rat.	Remarks.
1908.		
May 15	43	Feeding of cakes, each containing 0.0005 gm. thyroid, commenced.
18	43	
20	43	
23	41	
27	40	Morphine sulphate, 10 mgms., i. e., 0.25 mgm. per gm. rat. Survived.

B. THYROID OF GROUP 5 (IODOFORM); 0.3 PER CENT IODINE.

Date.	Weight of rat.	Remarks.
1908.		
May 15	36	Feeding of cakes, each containing 0.0005 gm. thyroid, commenced.
18	37	
20	37	
23	34	
25	34	Morphine sulphate, 4.76 mgms., i.e., 0.14 mgm. per gm. rat. Survived.
May 15	41	Thyroid as above.
18	39	
20	40	
23	39	
26	35	Morphine sulphate, 7. mgms., i.e., 0.2 mgm. per gm. rat. Survived.
May 15	44	Thyroid as above.
18	42	
20	43	
23	41	
24	41	
28	43	Morphine sulphate, 10.75 mgms., i.e., 0.25 mgm. per gm. rat. Died 5 hours.

C. THYROID OF GROUP 2 (NORMAL); 0.111 PER CENT IODINE.

1908.		
May 15	41	Feeding of cakes, each containing 0.0015 gm. thyroid, commenced.
18	39	
20	38	
23	38	
27	40	Morphine sulphate, 10 mgms., i.e., 0.25 mgm. per gm. rat. Died 2¼ hours.

D. THYROID OF GROUP 2 (NORMAL); 0.111 PER CENT IODINE.

1908.		
May 15	38	Feeding of cakes, each containing 0.003 gm. thyroid, begun.
18	37	
20	36	
23	35	
26	40	Morphine sulphate, 6.4 mgms., i.e., 0.16 mgm. per gm. rat. Survived.
May 15	45	Thyroid as above.
18	43	
20	43	
23	41	
24	41	
28	43	Morphine sulphate, 8.6 mgms., i.e., 0.2 mgm. per gm. rat. Died 3½ hours.

E. THYROID OF GROUP 3 (NORMAL); 0.106 PER CENT IODINE.

1908.		
May 15	54	Feeding of cakes, each containing 0.001 gm. thyroid, commenced.
18	52	
20	51	
23	50	
24	50	
27	51	Morphine sulphate, 12.75 mgms., i.e., 0.25 mgm. per gm. rat. Survived.

F. THYROID OF GROUP 5 (IODOFORM); 0.3 PER CENT IODINE.

1908.		
May 15	43	Feeding of cakes, each containing 0.001 gm. thyroid, commenced.
18	36	
20	37	
23	36	
24	36	
27	37	Morphine sulphate, 7.4 mgms., i.e., 0.2 mgm. per gm. rat. Died 5 hours.

G. CONTROLS.

Date.	Weight of rat.	Remarks.
1908.		
May 15	41	Feeding of cakes without thyroid commenced.
18	38	
20	37	
23	38	
26	40	Morphine sulphate, 13.6 mgms., i. e., 0.34 mgm. per gm. rat. Survived.
May 15	41	Cakes as above.
18	39	
20	37	
23	36	
28	36	Morphine sulphate, 14 mgms., i. e., 0.39 mgm. per gm. rat. Survived.
May 15	50	Cakes as above.
18	46	
20	48	
23	44	
27	44	Morphine sulphate, 17.6 mgms., i. e., 0.4 mgm. per gm. rat. Died 4 hours.

Summary.—These experiments may be summarized as follows:

	Gm. thyroid in each cake.	Percentage of iodine in thyroid.	Mgm. I in thyroid of each cake.	Loss of weight in per cent of original weight.	Fatal dose of morphine sulphate in mgm. per gm.	
					Recovered.	Died.
A	0.0005	0.111	0.00055	7.0	0.25	.....
B	.0005	.3	.0015	7.6	.20	0.25
C	.0015	.111	.00166	2.4	.....	.25
D	.003	.111	.00333	.0	.16	.20
E	.001	.106	.00106	5.5	.25	.....
F	.001	.3	.0030	14.0	.....	.20
G. Controls	.....	.....	.....	9.1	.39	.40

These experiments show that with equal amounts of thyroid containing different percentages of iodine those with the larger amounts of iodine caused the greater lowering of resistance to morphine; also that in order to obtain equal physiological effects it was necessary to feed much more of the iodine-poor thyroid. Loss of weight can not explain the increased susceptibility of the rats to morphine, for with but one exception there was no loss of weight greater than that which could be ascribed to the exclusive cracker diet.

SERIES B.

Twenty-three dogs were divided into three groups. There were six dogs in the first group (Group 6), nine in the second (Group 7), and eight in the third (Group 8). Each of the dogs of Group 6 received about 1.2 grams iodoform in capsules on two successive days; they were killed on the day following that on which they had received the second dose. The glands were weighed and dried as described under Series A.

Group.	Weight of thyroid fresh.	Weight of thyroid dried.	Per cent of water.	Per cent of iodine.
6 (iodoform)	12.40	3.20	74.2	0.21
7 (normal)	33.05	8.69	73.7	.10
8 (normal)	17.40	4.60	73.5	.12

The following experiments were performed with these thyroids and some of those of Series A.

A. THYROID OF GROUP 8 (NORMAL); 0.12 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
July 13	19.13	Feeding of cakes, each containing 0.001 gm. thyroid, commenced.
17	17.18	
21	17.80	Acetonitrile, 8.01 mgms., i. e., 0.45 mgm. per gm. mouse. Survived.
July 13	16.40	Thyroid as above.
17	15.89	
21	15.66	Acetonitrile, 8.61 mgms., i. e., 0.55 mgm. per gm. mouse. Died 1 hour.
July 13	14.51	Thyroid as above.
17	14.09	
21	12.73	Acetonitrile, 8.91 mgms., i. e., 0.7 mgm. per gm. mouse. Died 2½ hours.

B. THYROID OF GROUP 2 (NORMAL); 0.111 PER CENT IODINE.

1908.		
July 13	15.36	Feeding of cakes, each containing 0.001 gm. thyroid, commenced.
17	13.78	
21	12.45	Acetonitrile, 8.09 mgms., i. e., 0.65 mgm. per gm. mouse. Died about 4 hours.
July 13	12.81	Thyroid as above.
17	11.59	
21	11.25	Acetonitrile, 10.13 mgms., i. e., 0.9 mgm. per gm. mouse. Died 1 hour.

C. THYROID OF GROUP 6 (IODOFORM); 0.21 PER CENT IODINE.

1908.		
July 13	14.00	Feeding of cakes, each containing 0.001 gm. thyroid, commenced.
17	13.25	
21	12.17	Acetonitrile, 10.95 mgms., i. e., 0.9 mgm. per gm. mouse. Survived.
July 13	11.80	Thyroid as above.
17	10.59	
21	11.29	Acetonitrile, 15.81 mgms., i. e., 1.4 mgms. per gm. mouse. Survived.
July 13	13.78	Thyroid as above.
17	14.14	
21	14.30	Acetonitrile, 22.88 mgms., i. e., 1.6 mgms. per gm. mouse. Survived.
July 13	12.25	Thyroid as above.
17	12.36	
21	9.84	Acetonitrile, 18.70 mgms., i. e., 1.9 mgms. per gm. mouse. Died 1 hour.

D. THYROID OF GROUP 5 (IODOFORM); 0.3 PER CENT IODINE.

Date.	Weight of mouse.	Remarks.
1908.		
July 13	15.91	Feeding of cakes, each containing 0.001 gm. thyroid, commenced.
17	14.88	
21	14.90	Acetonitrile, 19.37 mgms., i. e., 1.3 mgms. per gm. mouse. Survived.
July 13	17.39	Thyroid as above.
17	16.33	
21	16.20	Acetonitrile, 30.78 mgms., i. e., 1.9 mgms. per gm. mouse. Survived.
July 13	14.52	Thyroid as above.
17	13.72	
21	12.63	
22	.....	Acetonitrile, 26.52 mgms., i. e., 2.1 mgms. per gm. mouse. Survived.
July 13	17.78	Thyroid as above.
17	16.40	
21	17.12	Acetonitrile, 41.09 mgms., i. e., 2.4 mgms. per gm. mouse. Died 3 hours.

E. CONTROLS.

1908.		
July 13	14.35	Feeding of cakes without thyroid commenced.
17	13.98	
21	13.53	Acetonitrile, 3.25 mgms., i. e., 0.24 mgm. per gm. mouse. Survived.
July 13	13.25	Cakes as above.
17	12.83	
21	12.96	Acetonitrile, 3.24 mgms., i. e., 0.25 mgm. per gm. mouse. Died 1 hour.
July 13	14.20	Cakes as above.
17	13.03	
21	11.50	
22	.....	Acetonitrile, 2.99 mgms., i. e., 0.26 mgm. per gm. mouse. Died 2½ hours.

SUMMARY.

	Gm. thyroid fed daily.	Percentage of iodine in thyroid.	Mgm. I in thyroid fed daily.	Fatal dose of acetonitrile in mgms. per gm.	
				Recovered.	Died.
A	0.001	0.12	0.0012	0.45	0.55
B	.001	.111	.00111	.....	.65
C	.001	.21	.0021	1.6	1.9
D	.001	.3	.0030	2.1	2.4
E, Controls	.....	.....	.....	.24	.25

The results are very similar to those obtained with the thyroid of Series A. The thyroid, the iodine content of which had been increased by the administration of iodoform, was much more active in protecting mice against acetonitrile than was that of the normal dogs.

GENERAL SUMMARY OF ABOVE EXPERIMENTS AND CONCLUSIONS.

The experiments described above show that when potassium iodide or iodoform is administered to dogs the thyroids of the latter contain a greatly increased percentage of iodine and also are much more active physiologically. This result occurred too quickly to admit of any explanation other than that the increased activity was due to the increased iodine content. It seems to us to show conclusively that thyroid rich in iodine is more active than thyroid poor in iodine simply on account of the iodine; in other words, that the iodine is the cause and not the result of the activity.

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LIST OF HYGIENIC LABORATORY BULLETINS OF THE PUBLIC HEALTH AND MARINE-HOSPITAL SERVICE.

The Hygienic Laboratory was established in New York, at the Marine Hospital on Staten Island, August, 1887. It was transferred to Washington, with quarters in the Butler Building, June 11, 1891, and a new laboratory building, located in Washington, was authorized by act of Congress, March 3, 1901.

The following *bulletins* [Bulls. Nos. 1–7, 1900 to 1902, Hyg. Lab., U. S. Mar.-Hosp. Serv., Wash.] have been issued:

*No. 1.—Preliminary note on the viability of the *Bacillus pestis*. By M. J. Rosenau.

No. 2.—Formalin disinfection of baggage without apparatus. By M. J. Rosenau.

*No. 3.—Sulphur dioxid as a germicidal agent. By H. D. Geddings.

*No. 4.—Viability of the *Bacillus pestis*. By M. J. Rosenau.

No. 5.—An investigation of a pathogenic microbe (*B. typhi murium* Danyz) applied to the destruction of rats. By M. J. Rosenau.

*No. 6.—Disinfection against mosquitoes with formaldehyd and sulphur dioxid, By M. J. Rosenau.

No. 7.—Laboratory technique: Ring test for indol, by S. B. Grubbs and Edward Francis; Collodium sacs, by S. B. Grubbs and Edward Francis; Microphotography with simple apparatus, by H. B. Parker.

By act of Congress approved July 1, 1902, the name of the "United States Marine-Hospital Service" was changed to the "Public Health and Marine-Hospital Service of the United States," and three new divisions were added to the Hygienic Laboratory.

Since the change of name of the Service the bulletins of the Hygienic Laboratory have been continued in the same numerical order, as follows:

*No. 8.—Laboratory course in pathology and bacteriology. By M. J. Rosenau. (Revised edition, March, 1904.)

*No. 9.—Presence of tetanus in commercial gelatin. By John F. Anderson.

No. 10.—Report upon the prevalence and geographic distribution of hookworm disease (uncinariasis or anchylostomiasis) in the United States. By Ch. Wardell Stiles.

*No. 11.—An experimental investigation of *Trypanosoma lewisi*. By Edward Francis.

*No. 12.—The bacteriological impurities of vaccine virus; an experimental study. By M. J. Rosenau.

*No. 13.—A statistical study of the intestinal parasites of 500 white male patients at the United States Government Hospital for the Insane; by Philip E. Garrison, Brayton H. Ransom, and Earle C. Stevenson. A parasitic roundworm (*Agamomermis culicis* n. g., n. sp.) in American mosquitoes (*Culex sollicitans*); by Ch. Wardell Stiles. The type species of the cestode genus *Hymenolepis;* by Ch. Wardell Stiles.

No. 14.—Spotted fever (tick fever) of the Rocky Mountains; a new disease. By John F. Anderson.

No. 15.—Inefficiency of ferrous sulphate as an antiseptic and germicide. By Allan J. McLaughlin.

*No. 16.—The antiseptic and germicidal properties of glycerin. By M. J. Rosenau.

*No. 17.—Illustrated key to the trematode parasites of man. By Ch. Wardell Stiles.

*No. 18.—An account of the tapeworms of the genus *Hymenolepis* parasitic in man, including reports of several new cases of the dwarf tapeworm (*H. nana*) in the United States. By Brayton H. Ransom.

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*No. 19.—A method for inoculating animals with precise amounts. By M. J. Rosenau.

*No. 20.—A zoological investigation into the cause, transmission, and source of Rocky Mountain "spotted fever." By Ch. Wardell Stiles.

No. 21.—The immunity unit for standardizing diphtheria antitoxin (based on Ehrlich's normal serum). Official standard prepared under the act approved July 1, 1902. By M. J. Rosenau.

*No. 22.—Chloride of zinc as a deodorant, antiseptic, and germicide. By T. B. McClintic.

*No. 23.—Changes in the Pharmacopœia of the United States of America. Eighth Decennial Revision. By Reid Hunt and Murray Galt Motter.

No. 24.—The International Code of Zoological Nomenclature as applied to medicine. By Ch. Wardell Stiles.

No. 25.—Illustrated key to the cestode parasites of man. By Ch. Wardell Stiles.

No. 26.—On the stability of the oxidases and their conduct toward various reagents. The conduct of phenolphthalein in the animal organism. A test for saccharin, and a simple method of distinguishing between cumarin and vanillin. The toxicity of ozone and other oxidizing agents to lipase. The influence of chemical constitution on the lipolytic hydrolysis of etheral salts. By J. H. Kastle.

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No. 31.—Variations in the peroxidase activity of the blood in health and disease. By Joseph H. Kastle and Harold L. Amoss.

No. 32.—A stomach lesion in guinea pigs caused by diphtheria toxine and its bearing upon experimental gastric ulcer. By M. J. Rosenau and John F. Anderson.

No. 33.—Studies in experimental alcoholism. By Reid Hunt.

No. 34.—I. *Agamofilaria georgiana* n. sp., an apparently new roundworm parasite from the ankle of a negress. II. The zoological characters of the roundworm genus *Filaria* Mueller, 1787. III. Three new American cases of infection of man with horse-hair worms (species *Paragordius varius*), with summary of all cases reported to date. By Ch. Wardell Stiles.

*No. 35.—Report on the origin and prevalence of typhoid fever in the District of Columbia. By M. J. Rosenau, L. L. Lumsden, and Joseph H. Kastle. (Including articles contributed by Ch. Wardell Stiles, Joseph Goldberger, and A. M. Stimson.)

No. 36.—Further studies upon hypersusceptibility and immunity. By M. J. Rosenau and John F. Anderson.

No. 37.—Index-catalogue of medical and veterinary zoology. Subjects: Trematoda and trematode diseases. By Ch. Wardell Stiles and Albert Hassall.

No. 38.—The influence of antitoxin upon post-diphtheritic paralysis. By M. J. Rosenau and John F. Anderson.

No. 39.—The antiseptic and germicidal properties of solutions of formaldehyde and their action upon toxines. By John F. Anderson.

No. 40.—1. The occurrence of a proliferating cestode larva (*Sparganum proliferum*) in man in Florida, by Ch. Wardell Stiles. 2. A reexamination of the type specimen of *Filaria restiformis* Leidy, 1880=*Agamomermis restiformis*, by Ch. Wardell Stiles. 3. Observations on two new parasitic trematode worms: *Homalogaster philippinensis*

n. sp., *Agamodistomum nanus* n. sp., by Ch. Wardell Stiles and Joseph Goldberger. 4. A reexamination of the original specimen of *Tænia saginata abietina* (Weinland, 1858), by Ch. Wardell Stiles and Joseph Goldberger.

*No. 41.—Milk and its relation to the public health. By various authors.

No. 42.—The thermal death points of pathogenic micro-organisms in milk. By M. J. Rosenau.

No. 43.—The standardization of tetanus antitoxin (an American unit established under authority of the act of July 1, 1902). By M. J. Rosenau and John F. Anderson.

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